3. D. Kh. Mutsenietse, V. K. Lusis, and G. Ya. Dubur, Khim. Geterotsikl. Soedin., No. 9, 1225-1228 (1982).
4. D. Ya. Tirzite, G. D. Tirzit, G. Ya. Dubur, and V. V. Kastron, Byull. Éksp. Biol., No. 9, 39-40 (1982).
5. C. Hansch, Drug Design, E. J. Ariens (ed.), New York (1971), pp. 271-342.
6. E. E. Knaus, H. Wynn, M. W. Wolowyk, and R. S. Ball, Acta Cryst., 43, 1734-1737 (1971).
7. H. Machleit, S. Roth, and P. Seeman, Biochim. Biophys. Acta, 225, 178-189 (1972).

SYNTHESIS AND PSYCHOTROPIC PROPERTIES OF 4-AMINO-3-CYANO-1,2-DIHYDROSPIRO(NAPHTHALENE-2,1'CYCLOPENTANE) DERIVATIVES

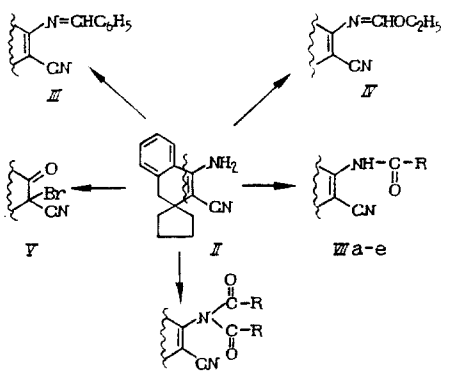
A. I. Markosyan, M. G. Oganisyan,
R. A. Kuroyan, R. S. Sukasyan,
É. M. Arzanunts, and I. S. Sarkisyan

UDC 615.31:547.659.1].012.1

It is reported in the literature that spirocyclic derivatives of naphthalene exhibit a high psychotropic activity [2-4]. It was therefore of interest to develop a method of synthesis of derivatives of 4-amino-3-cyano-1,2-dihydrospiro(naphthalene-2,1'-cyclopentane) and to examine the psychotropic properties of the synthesized compounds.

Condensation of cyclopentylidenemalononitrile with benzylmagnesium chloride gave 1-benzyl-1-dicyanomethylcyclopentane (I), whose cyclization in sulfuric acid led to the formation of 4-amino-3-cyano-1,2-dihydrospiro-(naphthalene-2,1'-cyclopentane) (II).

By condensation of aminonitrile II with benzaldehyde and orthoformic ester, the Schiff base III and the ethoxymethylene compound IV were obtained. Bromination of aminonitrile II in glacial acetic acid and subsequent treatment with a base gave 3-bromo-4-oxo-3-cyano-1,2,3,4-tetrahydrospiro(naphthalene-2,1'-cyclopentane) (V). the reaction of aminonitrile II with carboxylic acid chlorides was studied and the following patterns were discovered. The condensation of the above aminonitrile with acetyl chloride leads to the formation of the diacetylamino compound VI. when chloroacetyl chloride is used, depending on the amount of the reagent, a mono- (VIIa) or disubstituted product (VIb) can be obtained. In the reaction of aminonitrile II with propionyl, benzoyl and phenylacetyl chlorides, the monosubstituted compounds (VIIb-e) are the only products



R=CH3(VIIa), CH2Cl(VIb, VIIa), C2H5(VIIb), C3H7(VIIc), C6H5(VIId), C6H5CH2(VIIe)

The structure of the synthesized compounds was confirmed by IR, PMR and mass spectral and elemental analysis data. The results of the elemental analyses correspond to the calculated data.

A. L. Mndzhoyan Institute of Fine Organic Chemistry, Academy of Sciences of the Armenian SSR, Erevan. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 25, No. 8, pp. 26-28, August, 1991. Original article submitted October 22, 1990.

 0091-150X/91/2508-0536$12.50 © 1992 Plenum Publishing Corporation

EXPERIMENTAL (CHEMICAL)

The IR spectra of the compounds were run on a UR-20 spectrophotometer in mineral oil. The PMR spectra were obtained on a Varian T-60 spectrometer (USA, 60 MHz) in deuterated chloroform, using TMS as an internal standard. The mass spectra were run on an MKh-1320 spectrometer (USSR), using a system of direct introduction of the sample into the ionic source. The purity of the compounds was monitored on Silufol UV-254 plates (CSFR), using iodine as developing agent. The melting points were determined on a Boetius type heating stage.

1-Benzyl-1-diacyanomethylcyclopentane (I). A solution of 51.5 g (0.39 mole) of cyclopentylidenemalononitrile in 150 ml of dry ether was added dropwise with stirring to an ethereal solution of benzylmagnesium chloride, prepared from 14.4 g (0.6 mole) of magnesium chips and 76 g (0.6 mole) of benzyl chloride in 300 ml of absolute ether, while the temperature of the reaction mixture was maintained at 30-35°C. At the end of the addition, the mixture was stirred at this temperature for 5 h, was then cooled with ice water, and 180 ml of a 20% solution of sulfuric acid was added dropwise at 10-15°C. The mixture was stirred at room temperature to the complete decomposition of the complex. The organic layer was separated, washed with water, and dried over anhydrous sodium sulfate. After evaporation of the solvent, the residue was distilled under vacuum. Yield, 77 g (88%) of dinitrile I, bp 197°C/4 mm, mp 60-61°C (nonane), R_f 0.53 (hexane–ethyl acetate 3:1). $C_{15}H_{16}N_2$.

4-Amino-3-cyano-1,2-dihydrospiro(naphthalene-2,1'-cyclopentane) (II). Dinitrile I (5 g, 0.022 mole) was added in portions at 20-25°C, with stirring, to 10 ml of concentrated sulfuric acid. The mixture was stirred at this temperature for 2 h, and then poured onto ice. the precipitate was filtered off, transferred into a beaker, and was neutralized with stirring and cooling by ice water with a 20% solution of ammonia. The aminonitrile that separated out was extracted with ether, the extract was washed with water and dried over sodium sulfate. After the evaporation of the solvent, the residue was recrystallized from an ethanol–water (2:1) mixture. Yield 3.9 g (78%) of aminonitrile II, mp 79-81°C, R_f 0.52 (nonane–ethyl acetate 1:1). $C_{15}H_{16}N_2$, M^+.

4-Benzylideneamino-3-cyano-1,2-dihydrospiro(naphthalene-2,1'-cyclopentane) (III). A mixture of 2.2 g (0.01 mole) of aminonitrile II, 1.6 g (0.015 mole) of freshly distilled benzaldehyde, 0.1 g of para-toluenesulfonic acid and 20 ml of toluene was boiled for 3 h using a Dean-Stark adapter. The solvent was evaporated, and the residue was recrystallized from ethanol. Yield, 1.9 g (60.9%) of imine III, mp 120-122°C, R_f 0.60 (nonane–ethyl acetate 1:1). $C_{22}H_{20}N_2$.

4-Ethoxymethyleneimino-3-cyano-1,2-dihydrospiro(naphthalene-2,1'-cyclopentane) (IV). A mixture of 2.2 g (0.01 mole) of aminonitrile II, 4.6 g of orthoformic ester and 3 ml of acetic anhydride was boiled under reflux for 7 h. The excess of orthoformic ester and acetic anhydride was distilled off, and the residue was recrystallized from an ethanol–water (3:1) mixture. Yield, 0.8 g (28.6%) of imine IV, mp 51-53°C, R_f 0.57 (nonane–ethyl acetate 2:1). $C_{18}H_{20}N_2O$.

3-Bromo-4-oxo-3-cyano-1,2,3,4-tetrahydrospiro(naphthalene-3,1'-cyclopentane) (V). A 4.8 g portion (0.03 mole) of bromine was added dropwise with stirring, at 25-30°C to glacial acetic acid. The mixture was stirred for another 2 h at 30-35°C. The precipitate that separated out was filtered off, dissolved in absolute ethanol and neutralized with a 20% ammonia solution. The white crystals that separated out were filtered off, washed with water and recrystallized from abs. ethanol. Yield 2 g (6.5%) of bromide V, mp 144-145°C, R_f 0.53 (nonane–ethyl acetate 1:1). $C_{15}H_{14}BrNO$. M^+.

4-Diacetylamino-3-cyano-1,2-dihydrospiro(naphthalene-2,1'-cyclopentane) (VIa). A mixture of 2.2 g (0.01 mole) of aminonitrile II, 2.4 g (0.03 mole of acetyl chloride and 20 ml of dry benzene was boiled under reflux for 12 h. The solvent was evaporated and the residue was recrystallized from an ethanol–water (3:1) mixture. Yield, 2.5 g (79.9%) of the diacetylamino compound VIa, mp 104-106°C, R_f 0.66 (heptane–ethyl acetate 1:1). $C_{19}H_{20}N_2O_2$.

4-Dichloroacetylamino-3-cyano-1,2-dihydrospiro(naphthalene-2,1'-cyclopentane) (VIb) was obtained in a similar way as VIa from aminonitrile II and chloroacetyl chloride. Yield 2.5 g (66.3%), mp 126-127°C, R_f 0.65 (nonane–ethyl acetate 1:1). $C_{19}H_{18}Cl_2N_2O_2$.

4-Chloroacetylamino-3-cyano-1,2-dihydroxpiro(naphthalene-2,1'-cyclopentane) (VIIa). A mixture of 2.2 g (0.01 mole) of aminonitrile II, 1.1 g (0.01 mole) of chloroacetyl chloride

and 20 ml of benzene was boiled under reflux for 6 h. The solvent was evaporated and the residue was recrystallized from ethanol. Yield, 2.4 g (78.6%) of amide VIIa mp 156-158°C, R_f 0.46 (nonane–ethyl acetate 1:1). $C_{17}H_{17}ClN_2O$.

4-Propionylamino-3-cyano-1,2-dihydrospiro(naphthalene-2,1'-cyclopentane) (VIIb) was obtained in a similar way as VIIa from aminonitrile II and propionyl chloride. Yield 1.8 g (64.3%), mp 174-176°C, R_f 0.34 (nonane–ethyl acetate 1:1). $C_{18}H_{20}N_2O$.

4-Butyrylamino-3-cyano,1,2-dihydrospiro(naphthalene-2,1'-cyclopentane (VIIc) was obtained in a similar way as VIIa from aminonitrile II and butyryl chloride. Yield 1.2 g (41%), mp 147-149°C, R_f 0.41 (nonane–ethyl acetate 1:1). $C_{19}H_{22}N_2O$.

4-Benzoylamino-3-cyano-1,2-dihydrospiro(naphthalene-2,1'-cyclopentane) (VIId) was obtained in a similar way as VIIa from aminonitrile II and benzoyl chloride. Yield 1.9 g (59%), mp 213-215°C, R_f 0.44 (nonane–ethyl acetate 1:1). $C_{22}N_{20}N_2O$.

4-Phenylacetylamino-3-cyano-1,2-dihydrospiro(naphthalene-2,1'-cyclopentane) (VIIe) was obtained in a similar way as VIIa from aminonitrile II and phenylacetyl chloride. Yield 3 g (87%), mp 140-142°C, R_f 0.52 (nonane–ethyl acetate 1:1). $C_{23}H_{22}N_2O$.

EXPERIMENTAL (BIOLOGICAL)

Certain psychotropic properties of compounds III, V, VIa, b, VIIa, b, c, e were studied in experiments on white nonpedigree mice, each weighing 18-22 g and rats (150-180 g) of both sexes.

Using the accepted methods of investigation [1], the influence of these compounds (10, 50 and 100 mg/kg) was studied on the behavior, skin temperature, hexenal induced sleep (70 mg/kg), 5-hydroxytryptophan (5-HTP) induced hyperkinesis 9100 and 200 mg/kg), tryptamine induced toxicity (250 mg/kg) and phenamine induced toxicity (10 mg/kg) in mice, and of compounds III, V, VIa, b (100 mg/kg) on the depressant effects of reserpine in rats (2.5 mg/kg).

The influence of the naphthalenespirocyclopentanes on the deamination of serotonine (5-hydroxytryptamine, 5-HT) and phenylethylamine (PEA) by monoaminooxidase (MAO) from rat brain [5] was studied in experiments in vitro. The compounds were tested in a concentration of 1 μmole per 1 ml of the sample.

The daily toxicity dose of compound V administered intraperitoneally was determined in acute experiments on mice.

The experimental data were processed statistically according to Student-Fischer, Litchfield and Wilcoxon.

The results of the investigations showed that compounds III, V, VIa, b administered to mice intraperitoneally in a dose of 100 mg/kg cause an increase in the motoric activity, an exophthalm, and do not influence the skin temperature. Compounds VIIa, b, c, e do not substantially influence the behavior of mice, but have a hypothermal effect, which intensifies with increase in the dose. The most pronounced is the action of compound VIIa, which lowers the skin temperature of mice by 3.6°C in 1 h.

Compounds V, VIb, VIIb, c administered to mice in a dose of 100 mg/kg before introducing hexenal, potentiate its soporific action by a factor of 1.5-3. The highest intensification of the hexenal induced sleep (by 3 times) is caused by compound V. The remaining compounds do not substantially influence the soporific effect.

Of the compounds tested, only compounds III and V, administered to mice in a dose of 100 mg/kg subcutaneously 1 h before introducing reserpine, counteract the depressant effects of the neuroleptic (catalepsia and ptosis) by 50 and 100%, respectively.

Compounds V and VIa administered to mice in a dose of 100 mg/kg before introducing tryptamine intensify its toxicity in grouped animals by 50%. The remaining compounds do not influence the toxic effect of tryptamine.

All the compounds used in experiments on mice do not influence the hyperkinesis caused by injection of 5-HTP, and also the toxicity of phenamine under group conditions.

In experiments in vitro, compounds III, V, VIa, b inhibit to a certain extent the deamination of 5-HT and PEA. Compounds V and VIb, which inhibit the deamination of 5-HT and PEA by 50 and 45%, respectively ($p < 0.05$), have the most pronounced activity.

The acute daily toxicity dose (LD_{50}) of compound V, which was found to be most active in all experiments carried out on mice, is 520 mg/kg (444.4-608.4).

Thus, the experiments that have been carried out showed that in the series of naphthalenespirocyclopentanes studied. The oxobromide V exhibits some psychotropic properties: it causes an increase in motoric activity, intensification of tryptamine toxicity and hexenal induced sleep, and also has an antireserpine and antimonoaminooxidase action, which is characteristic of antidepressants. Compounds with various substituents at the nitrogen atom at the 4-position of naphthalenespirocyclopentane do not have noticeable psychotropic activity.

LITERATURE CITED

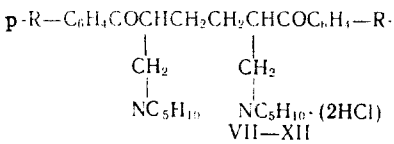
1. E. F. Lavretskaya, Pharmacological Regulation of Psychic Processes [in Russian], Moscow (1985), pp. 119-130.
2. US Patent 3953425; Chem. Abstr., 85, No. 23, P 177275 z (1976).
3. US Patent 3932425; Chem. Abstr., 85, No. 21, P 159760 z (1976).
4. US Patent 4010201; Chem. Abstr., 87, No. 3, P 22863 g (1977).
5. R. S. Safrazbekyan and R. S. Sukasyan, Biol. Zh. Armenii, 22, No. 10, 43-49 (1969).

SYNTHESIS OF 1,6-DIARYL-2,5-DIPERIDINOMETHYL-1,6-HEXANEDIONES AND THE BIOLOGICAL ACTIVITY OF THEIR DIHYDROCHLORIDES

G. A. Gevorgyan, L. M. Petrosyan,
N. A. Apoyan, Zh. S. Meklonyan,
L. K. Durgaryan, E. V. Vlasenko,
and O. L. Mndzhoyan

UDC 615.31:572.3/.012.1

We have previously reported on the synthesis and biological activity of dihydrochlorides of 1,6-diaryl-2,5-dihexamethyleneiminomethyl-1,6-hexanediones [5]. In continuation of these investigations, in the present work, we synthesized 1,6-diaryl-2,5-dipiperidino-1,6-hexanediones (I-VI) and studied the biological properties of their dihydrochlorides (VII-XII).



VII—XII

R=H (I, VII), MeO (II, VIII), EtO (III, IX), PrO (IV, X), BuO (V, XI); AmO (VI, XII)

Synthesis of compounds I-VI was carried out by aminomethylation of 1,6-diaryl-1,6-hexanediones with paraformaldehyde and piperidine hydrochloride in a dioxane medium. Compounds I-III and VI are water insoluble crystalline compounds, while IV and VI are thick oils, which decompose on distillation. By the action of an ethereal solution of HCl, bases I-VI were converted into dihydrochlorides VII-XII. In the IR spectra of I-VI, an absorption band of the carbonyl group is observed in the 1680-1685 cm^{-1} region.

In the PMR spectrum of compound I (CCl_4), signals of methylene group protons are observed: $(CH_2)_2$ (1.1-1.4 ppm) and CH_2N (2.1-2.8 ppm), and also of methine protons (3.4 ppm) and signals of aromatic protons at 7.28-7.95 ppm.

Besides this absorption, in the PMR spectra of compounds II-VI signals are also observed of alkoxyl group protons of the substituted aromatic ring.

EXPERIMENTAL (CHEMICAL)

The IR spectra were run on a UR-20 spectrophotometer in mineral oil.

A. L. Mndzhoyan Institute of Fine Organic Chemistry, Academy of Sciences of the Armenian SSR, Erevan.

Translated from Khimiko-faramatsevticheskii Zhurnal, Vol. 25, No. 8, pp, 28-30, August, 1991. Original article submitted November 2, 1990.

0091-150X/91/2508-0539$12.50 © 1992 Plenum Publishing Corporation