*Pharmaceutical Chemistry Journal, Vol. 28, No. 4, 1994*

# SYNTHESIS, STRUCTURE, AND BIOLOGICAL ACTIVITY OF DERIVATIVES OF [2,2]-PARA-CYCLOPHANE. 3.* 1-PYRIDYL(ARYL)-2-[2,2]-PARA-CYCLOPHAN-4-OYL)-ETHYLENES AND THEIR FUNGICIDAL ACTION

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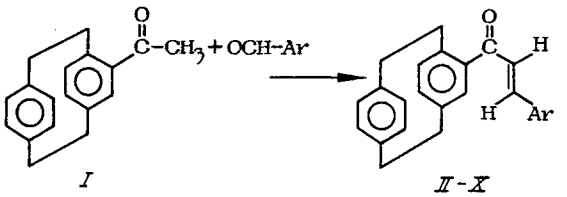
UDC 615.03.988/.514.38

Continuing our work [1, 2] on synthesis and study of the dependences of the pesticidal activity on the structure of derivatives of [2,2]-para-cyclophane, we obtained a series of 1,2-disubstituted ethylenes which include a di(para-xylylene) moiety and aryl or pyridyl radicals. By condensation of 4-acetyl-[2,2]-para-cyclophane (I) with formylpyridines or substituted benzaldehydes in the presence of sodium ethoxide in alcohol, we synthesized 1-[2-pyridyl-(II), 3-pyridyl-(III), 4-pyridyl-(IV), phenyl-(V), 4-methoxyphenyl-(VI), 3,4-dimethoxyphenyl-(VII), 4-dimethylaminophenyl-(VIII), 4-nitrophenyl-(IX), and 2-nitrophenyl-(X)]-2-{[2,2]-para-cyclophan-4-oyl} ethylenes.




*I* *II-X*

Ar=2-(II), 3-(III), 4-(IV) pyridyl, Ph (V), $C_6H_4OCH_3$-p, $C_6H_3(OCH_3)_2$-m, p (VII), $C_6H_4N(CH_3)_2$-p (VIII), $C_6H_4NO_2$-p (IX), $C_6H_4NO_2$-*o* (X).

The characteristics of the new compounds II-XI and their PMR spectra are presented in Tables 1 and 2. The high-resolution PMR spectra (400 MHz) for compounds II and III allow us to assign the signals for most of the protons in the multiproton system of the substituted ethylenes II-X obtained. The spectral data show that in all the compounds, both bulky radicals for the ethylene moiety are trans to each other, evidence for which comes from the high value of the spin–spin coupling constant for the two vicinal protons of the ethylene part (J = 15.6-16 Hz). These protons in compounds III-IX resonate as a pair of doublet signals at 7.46-7.6 ppm (the proton of the O=C–CH= moiety) and at 6.94-7.17 ppm (the proton of the =CHAr moiety). The difference between the centers of these two doublet pairs is about 0.5 ppm. When a nitro group is present in the ortho position of the aryl radical (compound X), this difference reaches 1.0 ppm, while in the case of an alpha-pyridyl substituent (compound II), both ethenyl protons become practically magnetically equivalent ($\Delta\delta$ = 0.09 ppm). As characteristic signals in this series of compounds we can also include the signals from the two aromatic protons (H-5 and H-7) and one aliphatic proton (H-2) of the para-cyclophane moiety of the molecule, which stand out as a result of the deshielding effect of the adjacent electron–acceptor group.

*For Communication 2, see [2].

Russian P. Lumumba International Friendship University, Moscow. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 28, No. 4, pp. 42-44, April, 1994. Original article submitted July 12, 1993.

0091-150X/94/2804-0267$12.50 

TABLE 1. Characteristics of Synthesized Compounds

| Compound | m.p. °C | IR spectrum, ν, cm−1 | Found/Calculated, % | | | Empirical formula | Yield, % |
|---|---|---|---|---|---|---|---|
| | | | C | H | N | | |
| II | 133—134 | 1673, 1648 sh., 1600 | 85,1/85,0 | 6,3/6,2 | 3,9/4,1 | $C_{24}H_{21}NO$ | 43 |
| III | 168—170 | 1663, 1648 sh., 1602 | 85,3/85,0 | 6,1/6,2 | 4,3/4,1 | $C_{24}H_{21}NO$ | 90 |
| IV | 166—168 | 1670, 1650 sh., 1615, 1593 | 84,9/85,0 | 6,4/6,2 | 4,0/4,1 | $C_{24}H_{21}NO$ | 70 |
| V | 172—174 | 1684 sh., 1664, 1622 sh., 1602 | 89,0/88,7 | 6,2/6,5 | — | $C_{25}H_{22}O$ | 61 |
| VI | 170—172 | 1687 sh., 1671, 1620 sh., 1599 | 84,7/84,8 | 6,3/6,5 | — | $C_{26}H_{24}O$ | 86 |
| VII | 171—173 | 1683 sh., 1662, 1612 sh., 1587 | 81,3/81,4 | 6,4/6,5 | — | $C_{27}H_{26}O_3$ | 82 |
| VIII | 123—124 | 1697 sh., 1685, 1655 | 85,0/85,0 | 7,4/7,1 | 3,6/3,7 | $C_{27}H_{27}NO$ | 26 |
| IX | 211—213 | 1682 sh., 1672, 1612, 1599, 1524, 1350 | 77,8/78,0 | 4,8/5,0 | 3,6/3,7 | $C_{25}H_{21}NO_3$ | 69 |
| X | 125—127 | 1687 sh., 1672 sh., 1658, 1610, 1537, 1354 | 78,3/78,0 | 4,9/5,0 | 3,4/3,7 | $C_{25}H_{21}NO_3$ | 17 |

The structure of the synthesized compounds is also confirmed by the IR spectral data (see Table 1), in which there is a very strong band for the stretching vibrations of the carbonyl group, appearing in the region 1662-1685 $cm^{-1}$. The absorption band for the ethylene moiety is observed as a shoulder at 1650-1648 $cm^{-1}$ in the case of the pyridyl derivatives II-IV and at 1610-1622 $cm^{-1}$ for compounds V-VII, IX.

In the mass spectra of compounds V-IX there are $M^+$ molecular ion peaks of high or maximum intensity, while for compounds III and X such peaks are of medium and low intensity, respectively (see experimental part). Characteristic for all the studied series of compounds is decomposition under electron impact with cleavage of the unsubstituted para-xylylene moiety with m/z 104, which is formed as a result of decyclization of the strained cyclophane system with respect to the bridging $-CH_2-CH_2$ bonds. This process is accompanied by the appearance of an ion peak $[M - 104]^{+\cdot} = F_1$ of high or medium intensity. The $F_1$ species, containing the carbonyl functional group, then ejects the CO and CHO group. We should also note one more fragmentation pathway common to all the studied compounds, involving rupture of the C−C bond between the keto group and the ethylene group in the molecular ion, which leads to formation of the ion peaks $[M - ArC_2H_2]^{+\cdot}$ and $[ArC_2H_2]^{+\cdot}$. In the mass spectra of the compounds containing the functional groups, we also observe ion peaks which arise upon dissociative ionization of the original molecule with characteristic detachment of the simple species ($CH_3$, $OCH_3$, $NO_2$).

Tests of the pesticidal properties of the synthesized compounds showed that none of them exhibit antibacterial activity on such a test specimen as the bacteria *Xanthomonas malvacearum*. As the fungicides, in the *in vitro* tests (Table 3) all the compounds exhibit a weak effect, and this class of unsaturated ketones is probably not promising for the search for fungicides. However, considering the high fungicidal activity of 4-bromoacetylcyclophanes and the series of their quaternary salts with pyridines [2], the obtained ethylene ketones II-X are potentially of interest as intermediates for synthesis of drugs with more pronounced pesticidal properties (for example, by means of their halogenation at the ethylene bond).*

## EXPERIMENTAL

The characteristics of the instruments and methods for physicochemical monitoring and analysis are given in the preceding papers [1, 2].

**General Technique for Synthesis of 1-Aryl(pyridyl)-2-{[2,2]-para-cyclophan-4-oyl}ethylenes (II-X).** A solution of sodium ethoxide [prepared from 0.09 g (3.9 mmoles) sodium and 2.3 ml ethanol] was added with stirring to a solution of 0.5 g (2 mmoles) 4-acetyl-[2,2]-para-cyclophane (I) and 2.4 ml (2 mmoles) (hetero)aromatic aldehyde in 30 ml absolute ethanol. The mixture was heated for 0.5-1.5 h and then cooled. The residue was separated, washed with 100 ml water, and crystallized from alcohol. When formylpyridines were used, the reaction mixture was evaporated down to half volume, treated with a mixture of 30 ml water and 15 g ice, and then with 10 ml of a saturated ammonium chloride solution. The ethylene ketones were extracted with chloroform; the extract was dried, and after driving off the solvent it was crystallized from heptane. We obtained

*We duly express our appreciation to our coworkers at the Scientific Research Institute of Chemical Plant Protection, V. I. Abelentsev and T. I. Solov'eva, for conducting the bioactivity tests.

TABLE 2. PMR Spectra of Compounds II-X

| Compound | Chiemical shift, δ, ppm | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | aromatic protons of para-cyclophane | | | | H-1, 2, 9, 10 | COCH=CH[3] | protons of substituent R (spin–spin coupling constant J, Hz) | | | | |
| | 5 | 7[1] | 8 | 12, 13, 15, 16 | | | 2 | 3 | 4 | 5 | 6 |
| II[2] | 7,0 | 6,66 | 6,38 | 6,55, 3H; 6,61 | 3,26; 1H; 3,15, 3H; 3,02, 2H; 2,93, 1H | 7,65 and 7,56 | — | 7,43(7,6) | 7,69(7,6) | 7,24(7,6 and 4,6) | 8,65(4,6 and 1,5) |
| III[2] | 6,91 | 6,7 | 6,38 | 6,57, 3H, 6,61 | 3,27, 4H; 3,04, 2H; 2,94, 1H | 7,54 and 7,17 | 8,78 | — | 7,88(7,9) | 7,34(7,9) | 8,61(4,9) |
| IV | 6,86 | 6,64 | 6,26—6,55 | | 2,9—3,2 | 7,46, 7,15 | 8,61 br. | 7,33 | — | 7,33 | 8,61 br. |
| V | 6,92 | 6,7 | 6,36 | 6,55 | 2,8—3,3 | 6,55 and 7,12 | | 7,3—7,6 | | | |
| IV[4] | 6,9 | 6,7 | 6,4 | 6,54 | 2,9—3,3 | 7,53 and 6,96 | 7,5(8,4) | 6,94 | — | 6,94 | 7,5 |
| VII[5] | 6,9 | 6,64 | 6,36 | 6,54 | 2,95—3,3 | 7,52 and 6,94 | 7,0 | — | — | 6,93(1,5) | 7,08 |
| VIII[6] | 6,92 | 6,64 | 6,4 | 6,56 | 2,9—3,3 | 7,5 and 6,93 | 7,45(8,6) | 6,66 | — | 6,66 | 7,45 |
| IX | 6,94 | 6,6 | 6,35 | 6,52 | 2,9—3,3 | 7,6 and 7,15 | 7,66 | 8,22(8,6) | — | 8,22 | 7,66 |
| X | 6,95 | 6,63 | 6,4 | 6,52 | 2,9—3,3 | 7,9 and 6,94 | — | 8,0(7,4) | 7,4—7,73 | | |

[1] $J_{7,8}$ = 7.6-7.9 Hz; $J_{5,7}$ = 1.5-1.8 Hz.

[2] H-13 for compounds II and III at 6.61 ppm; $J_{12,13}$ = 7.6-7.9 Hz; for all the compounds, H-2 resonates at 3.7-3.79 ppm; J = 10.4 and 2.1 Hz.

[3] J = 15.6-16 Hz.

[4] 3.9 ppm, $CH_3$.

[5] 3.93 ppm, 2 × $CH_3$.

[6] 2.98 ppm, 2 × $CH_3$.

TABLE 3. Fungicidal Activity *in Vitro* for Compounds II-X

| Test specimen[1] | Suppression of growth of mycelium of fungus, %[2] | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | II | III | IV | V | VI | VII | VIII | IX | X |
| Sc. sclerotiorum | 38 | 20 | 10 | 5 | 20 | 5 | 23 | 0 | 13 |
| F. graminearum | 22 | 16 | 5 | 0 | 5 | 5 | 0 | 0 | 5 |
| V. inaegualis | 33 | 0 | 17 | 0 | 0 | 23 | 10 | 0 | 0 |
| H. sativum | 23 | 23 | 0 | 0 | 10 | 0 | 0 | 0 | 0 |
| Rh. solani | 35 | 10 | 5 | 5 | 0 | 23 | 18 | 0 | 25 |

[1]For the complete name of the specimen, see [1, 2].
[2]Compared with the reference TMTD (100%).

compounds II-X as pale beige, yellow, or greenish yellow crystals. The characteristics of compounds II-X, their PMR spectra, and the results of biological testing are presented in Tables 1-3, respectively.

Mass spectra of compounds III, V-X, m/z (relative intensity). Symbols for the common fragments: $F_1$ = $(M-CH_2=C_6H_4=CH_2)^{+\cdot}$, $F_2 = (F_1 - CO)^+$, $F_3 = (F_1 - HCO)^+$, $F_4 = (M-ArCH=CH)^+$, $F_5 = (ArCH=CH)^+$. Ketone III: $M^+$ 339(42), $[M-HCN]^+$ 312(2), $[M-CO]^+$ 311(3), 253(5), 252(5), 251(10), 250(42), $F_1 + F_4$ 235(15), $[F_1 - CO]^+$ 207(22), 206(27), 172(15), 146(35), 119(21), 105(29), 104(100). Ketone V: $M^+$ 338(100), 337(4), $F_4$ 235(16), 233(73), 219(16), $F_2$ 206(21), $F_3$ (205), 204(9), 202(17), 191(30), 192(12), 189(20), 178(11), 165(11), 143(60), 128(12), 115(12), 104(82), 105(87), $F_5$ 103(44), 91(45), 78(24), 77(30). Ketone VI: $M^+$ 368(100), $F_1$ 264(33), $F_2$ 236(5), $F_3 + F_4$ 235(9). Ketone VII: $M^+$ 398(74), $[M-CH_3]^{+\cdot}$ 383(4), $[M-OCH_3]^{+\cdot}$ 367(13), $F_1$ 294(50), 293(21), $[F_1 - CH_3]$ 279(11), $F_2$ 266(8), $F_3$ 265(9), 263(17), $F_4$ 235(15), 191(8), 178(8), $F_5$ 163(2), $[F_1 - COC=CH]^{+\cdot}$ 151(100), 128(12), 115(6), 105(18), 104(43), 103(19), 91(8), 78(12), 77(11). Ketone VIII: $M^+$ 381(100), $[M-CH_3]^{+\cdot}$ 361(1), $F_1$ 277(73), 276(30), $[F_1 - CH_3]$ 262(3), $F_2$ 249(10), $F_3$ 248(15), $F_4$ 235(3), 234(9), 205(8), 191(8), 144(7), 134(70), $[F_5 + H]^+$ 121(12), 105(5), 104(28), 103(12), 91(3), 78(8), 77(6). Ketone IX: $M^+$ 383(90), $[M-NO_2]^{+\cdot}$ 337(100). Ketone X: $M^+$ 383(3), $[M-OH]^+$ 366(3), $[M-NO_2]^+$ 337(4), $[M-103]^+$ 280(100).

## REFERENCES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