SYNTHESIS AND ANTIOXIDANT ACTIVITIES OF 2-METHYL-5-OXO-1,4-DIHYDROINDENO[1,2-b]PYRIDINES

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Cycloalkyl esters of 4-aryl- and 4-cinnamyl-2-methyl-5-oxo-1,4-dihydroindeno[1,2b]pyridine-3-carboxylic acids were synthesized. Their antioxidant activities, which are most pronounced for the 4-(2-nitrophenyl) derivatives, were determined with respect to the inhibition of the autooxidation of methyl oleate.

We have previously ascertained [1, 2] that some 5-oxo-1,4-dihydroindeno[1,2-b]pyridines (I) - polycyclic analogs of 1,4-dihydropyridine - have antioxidant properties. Although 3substituted compounds of this type are known [3-7], 3-(cycloalkyloxycarbonyl) derivatives have not been synthesized hitherto. In the present paper we describe the synthesis of such compounds and their spectroscopic characteristics; we also investigated their oxidation and antioxidant activities.

New derivatives I were synthesized by a general method [3]. Their UV spectra are basically identical to the spectra of the previously synthesized compounds, and only the long-wave absorption band that is characteristic for the synthesized compounds, which vanishes when they are oxidized, is therefore presented in Table 1. Absorption bands of CO and NH bonds, the positions of which are in agreement with the previously published data [4-7], are clearly revealed in the IR spectra (Table 1).

The PMR spectra of I (Tables 2 and 3) confirm their structure. An average shift of 0.1 ppm of the signal of the 4-H proton to weak field is observed in the spectra of 4-(2-nitro-phenyl)-substituted dihydroindenopyridines, which indicates the direct effect of the NO<sub>2</sub> group on this proton. The well-known facile photochemical intramolecular disproportionation of the one-ring analogs of I, viz., 4-(2-nitrophenyl)-1, 4-dihydropyridines [8], for which a weak-field shift of the 4-H signal in various solvents is also observed (for example, see [9]), is also in agreement with this effect. The observed (in some cases) splitting or broadening of the signal of the proton (Ic, e, i; Table 2) is probably explained by long-range spin-spin coupling. One-ring 4-(2-nitrophenyl)-1, 4-dihydropyridines have been investigated as cardiovascular agents [9, 10]; the results of a study of their three-ring analogs I will be published separately.

4-(2-Nitrophenyl)-substituted Ic, m are oxidized by chloranil with greater difficulty than their 4-phenyl analogs (the reaction rate constants for Ic, m are, respectively, 0.10 and 0.22 liter-mole<sup>-1</sup>-sec<sup>-1</sup>, as compared with 0.82 liter-mole<sup>-1</sup>-sec<sup>-1</sup> for In [5]).

The antioxidant activities of the synthesized dihydroindenopyridines were determined with respect to inhibition of the autooxidation of methyl oleate by the method in [11] (Table 4). Their activities are usually higher than the activity of the corresponding 1,4-dihydropyridine derivatives. It may be assumed that one of the factors that explain this phenomenon is the greater coplanarity of the molecules in the case of dihydroindenopyridines as compared with resulting inhibitor radical and thus decreases the possibility of initiation of new chains of oxidation by this radical. The latter is confirmed by the existence of a rectilinear dependence of the antioxidant activity on the dihydroindenopyridine concentration. In addition, the presence of a substituent in the 4 position of the I molecule has virtually no effect on the activity, although in the case of 1,4-dihydropyridines the presence in the 4 position of even an electron-donor substituent leads to a significant decrease or total loss in the activity. The presence of an o-nitrophenyl substituent in the 4 position leads to a significant increase in the antioxidant activity, which, as has already been noted [2], is specifically peculiar only to o-nitrophenyl derivatives (compare Ia, c, d, In, m, and II,

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| pund  |                                |  | °C             | Long-wave<br>maximum<br>in the UV                 | <i>v</i> , cm <sup>-1</sup> |                   | Found, % |     | %   | Empirical  | Calc., % |     |     | Yield, |
|-------|--------------------------------|--|----------------|---|-----------------------------|-------------------|----------|-----|-----|--|----------|-----|-----|--------|
| Compo | Rı                             | R <sup>2</sup>                                   | тр, С          | spectrum: $\lambda_{\max}$ , nm $(\log \epsilon)$ | C=0                         | NH                | с        | н   | N   | formula  | с        | н   | N   | %      |
| Ia    | 1-Adaman-                      | C <sub>6</sub> H <sub>5</sub>                    | 300 (dec.)     | 485 (3,45)  | 1704,                       | 3275              | 79,5     | 6,6 | 2,8 | C <sub>30</sub> H <sub>29</sub> NO <sub>3</sub>  | 79,8     | 6,5 | 3,1 | 67     |
| Ip    | tyloxy<br>1-Adaman-            | C <sub>6</sub> H <sub>4</sub> CH <sub>3</sub> -2 | 235—238        | 490 (3,46)  | 1701,                       | 3265              | 79,7     | 6,4 | 2,9 | $C_{31}H_{31}NO_3\\$                             | 80,0     | 6,7 | 3,0 | 23     |
| Ic    | tyloxy<br>1-Adaman-            | C <sub>6</sub> H <sub>4</sub> NO <sub>2</sub> -2 | 157— .60       | 485 (3,30)  | 1672<br>1698,               | 3260              | 71,9     | 5,9 | 5,8 | $C_{30}H_{28}N_2O_5$                             | 72,6     | 5,7 | 5,7 | 88     |
| Id    | tyloxy<br>1-Adaman-            | C <sub>6</sub> H <sub>4</sub> NO <sub>2</sub> -4 | 210 (dec.)     | 480 (3,29)  | 1690<br>1705,               | 3260              | 72,0     | 5,3 | 5,9 | $C_{30}H_{28}N_2\dot{O}_5$                       | 72,6     | 5,7 | 5,7 | 41     |
| Ie    | tyloxy<br>1-Adaman-            | $C_6H_4F-2$                                      | 300303         | 485 (3,46)  | 1675<br>1691,               | 3263              | 76,4     | 6,1 | 2,9 | C <sub>30</sub> H <sub>28</sub> FNO <sub>3</sub> | 76,7     | 6,0 | 3,0 | 81     |
| lf    | tyloxy<br>1-Adaman-            | CH=CHC <sub>6</sub> H <sub>5</sub>               | 320 (dec.)     | 485 (3,44)  | 1670<br>1703,               | 3282              | 79,8     | 6,8 | 3,0 | $C_{32}H_{31}NO_3$                               | 80,5     | 6,5 | 2,9 | 79     |
| I.g.  | tyloxy<br>Bornyloxy            | C <sub>6</sub> H <sub>4</sub> NO <sub>2</sub> -2 | 267—270        | 485 (3,32)  | 1679<br>1710,<br>1700,      | 3218              | 71,9     | 6,3 | 6,0 | $C_{30}H_{30}N_{2}O_{\bf 5}$                     | 72,3     | 6,1 | 5,6 | 76     |
| Ιh    | Isoborny10xy                   | $C_6H_5$   | 265—267        | 475 (3,46)  | 1679<br>1703,<br>1687       | 3265              | 79,4     | 7,0 | 3,2 | $C_{30}H_{31}NO_{3}$                             | 79,4     | 6,9 | 3,1 | 74     |
| li    | Menthy10xy                     | C <sub>6</sub> H <sub>4</sub> CH <sub>3</sub> -2 | 168170         | 485 (3,48)  | 1698,                       | 3285              | 78,9     | 7,4 | 3,1 | $C_{31}H_{35}NC_{3}$                             | 79,3     | 7,5 | 2,9 | 82     |
| lj    | Menthyloxy                     | CH=CHC <sub>6</sub> H <sub>5</sub>               | 158—161        | 480 (3,45)  | 1700,                       | 3260              | 79,4     | 7,5 | 2,8 | $C_{32}H_{35}NO_{3}$                             | 79,8     | 7,3 | 2,9 | 67     |
| Ik    | Cyclohexyl-                    | C <sub>6</sub> H <sub>4</sub> NO <sub>2</sub> -2 | 160—163        | 485 (3,38)  | 1713,                       | 3268              | 69,5     | 5,5 | 6,7 | $C_{26}H_{24}N_2O_5$                             | 70,3     | 5,4 | 6,3 | 35     |
| 11    | OXY<br>CH3                     | C <sub>6</sub> H <sub>4</sub> NO <sub>2</sub> -2 | 267—270        | 490 (3,44)  | 1690,                       | 3285              | 69,5     | 4,5 | 7,9 | $C_{21}H_{16}N_2O_4$                             | 70,0     | 4,5 | 7,8 | 75     |
| Im    | OC <sub>2</sub> H <sub>5</sub> | C <sub>6</sub> H <sub>4</sub> NO <sub>2</sub> -2 | 240—242        | 485 (3,35)  | 1712, 1678                  | 3285              | 67,2     | 5,0 | 7,0 | $C_{22}H_{18}N_2O_5$                             | 67,7     | 4,7 | 7,2 | 70     |
|       | I                              | TABLE 2. 1                                       | ı<br>PMR Spect | I<br>ra of I (                                    | in CD                       | <br>)Cl₃)         | ļ        | l   | ļ   | I  | t l      |     |     | ł      |
|       |                                | Com-<br>pound                                    | L              |   |                             | <sup>5,</sup> ppm |          |     | ·   |  |          |     |     |        |

| Ia <sup>♥</sup>   | 1.58-2.06 (15H, m adamantyl); 2.44 (3H, s, 2-CH <sub>3</sub> ); 4.83 (1H, s, 4-H); 7.05-   |
|-------------------|--|
| Ιb                | $(1,47)$ (9H,in, $C_{6}$ (13, |
| lc                | $1,53-2,00$ (15H, m, admantyl); 2,43 (3H, d, $J=0.9$ Hz, $2\text{-CH}_3$ ); 6,00 (1H, d, $J=0.9$ Hz, $4\text{-H}$ ) 6.97 (1H, br s, NH), 7,00-7.95 (8H, m, -CeHand -CeH-CO)  |
| Id                | $1.55-2.10$ (15H, m, adamantyl); 2.49 (3H, s, 2-CH <sub>3</sub> ); 5.06 (1H, s, 4-H); 6.86 (1H, br s NH); 7.05-7.40 (4H, m, $-C_{c}H_{4}CO-$ ); 7.50 (2H, d, $J=8.0$ Hz.   |
| Ie <b>*</b>       | 2'-H—C <sub>6</sub> H <sub>4</sub> NO <sub>2</sub> ): 8,11 (2Hd, $J=8,0$ Hz, 3'-H—C <sub>6</sub> H <sub>4</sub> NO <sub>2</sub> )<br>1,16—2,10 (15H, m, adamantyl); 2,33 (3H, s, 2-CH <sub>3</sub> ); 4,37 (1H, d, $J=2,0$ Hz, 4-H); 7,1—7,6 (8H,m, —C <sub>6</sub> H <sub>4</sub> —and—C <sub>6</sub> H <sub>4</sub> CO—); 9,74 (1H, br s, NH)  |
| Ig                | $0.38-2.30$ (16H, m, bornyl); 2.49 (3H, d, $J=0.9$ Hz, 2-CH <sub>3</sub> ); 4.70-4.90 (1H, m, COOCH); 6.10 (1H, br s, 4H); 6.95 (1H, br s, NH); 7.00-7.90 (8H, m, -C_6H_4-   |
| Ih                | and $-C_6H_4CO_{-}$ )<br>0,25–1,85 (16H,m, isoborny1); 2,54 (3H, d, $J=0.9$ Hz 2-CH <sub>3</sub> ); 4,45–4,67 (1H, m COOCH); 4,96 (1H, br s, 4-H); 6,68 (1H, br s, NH); 6,90–8,50 (9H, m, C <sub>6</sub> H <sub>5</sub>  |
| Ii                | $0.20-2.15$ (18H,m, methyl); 2.44 (3H,d , $J=4.0$ Hz 2-CH <sub>3</sub> ); 2.69 (3H, d , $J=3.6$ Hz, $CH_3$ —Ph); 4.40—4.80 (1H,m, COOCH); 5.08 (1H, d, $J=3.6$ Hz, 4H);  |
| Ik                | 6,90–7,50 (9H, m, $-C_6H_4-$ , $-C_6H_4CO-$ and NH)<br>0,70–1,90 (10H, m, cyclohexyl); 2,45 (3H, s, 2-CH <sub>3</sub> ); 4,40–4,80 (1H, m, COOCH); 6,01 (1H, s, 4-H); 7,00–7,95 (9H, m, $-C_6H_4-$ , $-C_6H_4CO-$ and NH)  |
| lm                | 0,70-1,90 (10H, m, cyclohexyl); 2,45 (3H, s, 2-CH <sub>3</sub> ); 4,40-4,80 (1H,m,<br>COOCH); 601 (1H, -4 H); 200 795 (9H, m, C-H, CO, 200 NH)   |
| In†               | 1,09 (3H, $J=7,0$ Hz, CH <sub>3</sub> ester) ; 2,50 (3H, s, 2-CH <sub>3</sub> ); 4,02 (2H, bf, $J=7,0$ Hz, COOCH <sub>2</sub> ); 4,99 (1H, s, 4-H); 6,50 (1H, br s, NH); 6,95–7,40 (9H, m, C <sub>6</sub> H <sub>5</sub> and   |
|                   | $-C_6H_4CO-)$  |
| *In C             | $DC1_{3}$ - $D_{6}$ - $DMSO$ .   |
| <sup>†</sup> In t | his case $R^1 = OC_2H_5$ , and $R^2 = C_6H_5$ ; see [3] for the prep-  |

aration of this compound.

i, o in Table 4). The presence in the composition of the substituent in the 3 position of a more bulky adamantyl group leads to a decrease in the activity (compare In, a, as well as Im, c, in Table 4). The specificity of the antioxidant activity of o-nitrophenyl derivatives will serve as the subject of a separate communication.

TABLE 3. Chemical Shift of the 4-H Proton of I (d<sub>6</sub>-DMSO)

| Compound        | δ, ppm |
|-----------------|--------|
| ln              | 4,86   |
| Jo <sup>*</sup> | 4,94   |
| Im              | 5,71   |
| Id              | 4,82   |
| Ic              | 5,74   |
| Ii              | 4,89   |
| Ik              | 5,82   |

\*In this case  $R^1 = OC_2H_5$ , and  $R^2 = 4 - O_2NC_6H_4$ ; see [3] for the preparation of this compound.

TABLE 4. Antioxidant Activities of 1,4-dihydroindeno[1, 2-b]pyridine Derivatives (I) in Methyl Oleate at 50°C

| Compound   | Antioxidant activity  |  |  |  |  |  |
|--|---|--|--|--|--|--|
|  | $c=7.5\times$ $\times10^{-4}$ M   | $\begin{array}{c} c=3,0\times\\ \times 10^{-3} \text{ mole/liter} \end{array}$ |  |  |  |  |
| Ip<br>In<br>Ia<br>Im<br>Ic<br>Ig<br>I1<br>Io<br>Id<br>Ii | $ \begin{array}{c} 11,5\\11,0\\7,2\\48,0\\28,0\\25,0\\20,0\\-\\-\\4,9\\-\end{array} $ | + ×10-3 mole/liter   |  |  |  |  |
| *In this   | case R <sup>1</sup> =   | = $OC_2H_5$ , and  |  |  |  |  |

 $R^2 = H$ ; see [4] for the preparation of this compound.

## EXPERIMENTAL

The UV spectra of solutions of the compounds in ethanol were recorded with a Specord UV-vis spectrophotometer. The IR spectra of suspensions of the compounds in mineral oil were recorded with a Perkin-Elmer-580B spectrometer. The PMR spectra were recorded with a Brucker WH-90/DS spectrometer.

4-Aryl-2-methyl-5-oxo-1,4-dihydroindeno[1,2-b]pyridines (I). A 0.05-mole sample of the corresponding ester of the  $\beta$ -aminocrotonic acid or the acetylacetone imine was added to a refluxing solution of 0.05 mole of the 2-arylidene- or 2-cinnamylidene-1,3-indandione in 100 ml of glacial acetic acid, and the mixture was refluxed for 1-5 min. It was then cooled, and the precipitated dark-red substance was crystallized from acetic acid or dioxane-dimethyl-acetamide (1:1).

The oxidation of compounds of the I type with chloranil was carried out by the method in [5].

## LITERATURE CITED

- D. Ya. Rubene, I. É. Kirule, É. A. Bisenieks, and G. D. Tirzit, Sixth Conference of Biochemists of the Baltic Republics, The Belorussian SSR, and Leningrad [in Russian], Zinatne, Riga (1981), p. 202.
- 2. I. É. Kirule, D. Ya. Rubene, É. A. Bisenieks, G. D. Tirzit, and G. Ya. Dubur, Khim. Geterotsikl. Soedin., No. 3, 416 (1982).
- 3. V. Petrow, J. Saper, and B. Sturgeon, J. Chem. Soc., No. 9. 2134 (1949).
- 4. É. I. Stankevich and G. Ya. Vanag, Dokl. Akad. Nauk SSSR, 140, 607 (1961).
- 5. Ya. R. Uldrikis, A. O. Kumerova, and G. Ya. Dubur, Khim. Geterotsikl. Soedin., No. 5, 691 (1973).
- 6. J. N. Chatterjae, S. C. Shaw, and S. N. Singh. J. Indian Chem. Soc., 55, 149 (1978).
- B. A. Vigante, Ya. Ya. Ozols, and G. Ya. Dubur, Izv. Akad. Nauk Latv. SSR, Ser. Khim., No. 6, 707 (1980).
- 8. A. J. Berson and E. Brown, J. Am. Chem. Soc., 77, 447 (1955).
- 9. R. Tacke, A. Bentlage, R. Towart, H. Meyer, F. Bossert, W. Vater, and K. Stoepel, Z. Naturforsch., 35b, 494 (1980).
- 10. F. Bossert and W. Vater, Naturwissenschaften, 58, 578 (1971).
- 11. E. B. Burlakova, B. G. Dzantiev, A. K. Zefirova, G. B. Sergeev, and N. M. Émanuél', Izv. Vuzov SSSR, Khim. Khim. Tekhnol., No. 2, 265 (1960).