

## SYNTHESIS AND CHEMICAL PROPERTIES OF 8-ARYL-7-ACYL-1,6-DIMETHYL-6-HYDROXY-4-CYANO-5,6,7,8-TETRAHYDRO-3(2H)-ISOQUINOLINONES AND ISOQUINOLINETHIONES

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*8-Aryl-7-acetyl-1,6-dimethyl-6-hydroxy-4-cyano-5,6,7,8-tetrahydro-3(2H)-isoquinolinones and -isoquinolinethiones and their sodium salts were obtained by the reaction of cyanoacetamide and cyanothioacetamide with 3-aryl-2,4-diacetyl-5-methyl-5-hydroxycyclohexanones in basic medium. 8-Aryl-7-acetyl-6-methoxycarbonyl-1,6-dimethyl-4-cyano-5,6,7,8-tetrahydro-3(2H)-isoquinolinones were obtained by the reaction of acetyl chloride and the above isoquinolinone sodium salts. The reaction of iodoacetamide and the above isoquinolinethione sodium salts yielded 8-aryl-7-acetyl-3-carbamoylmethylthio-1,6-dimethyl-4-cyano-5,6,7,8-tetrahydroisoquinolines, which were cyclized into 1-amino-6-aryl-7-acetyl-2-carbamoyl-5,8-dimethyl-8-hydroxy-6,7,8,9-tetrahydrothiophene[2,3-c]isoquinolines in basic medium.*

The cardiovascular activity of alkyl-substituted 5,6,7,8-tetrahydro-3(2H)-isoquinolinones is well known [1].

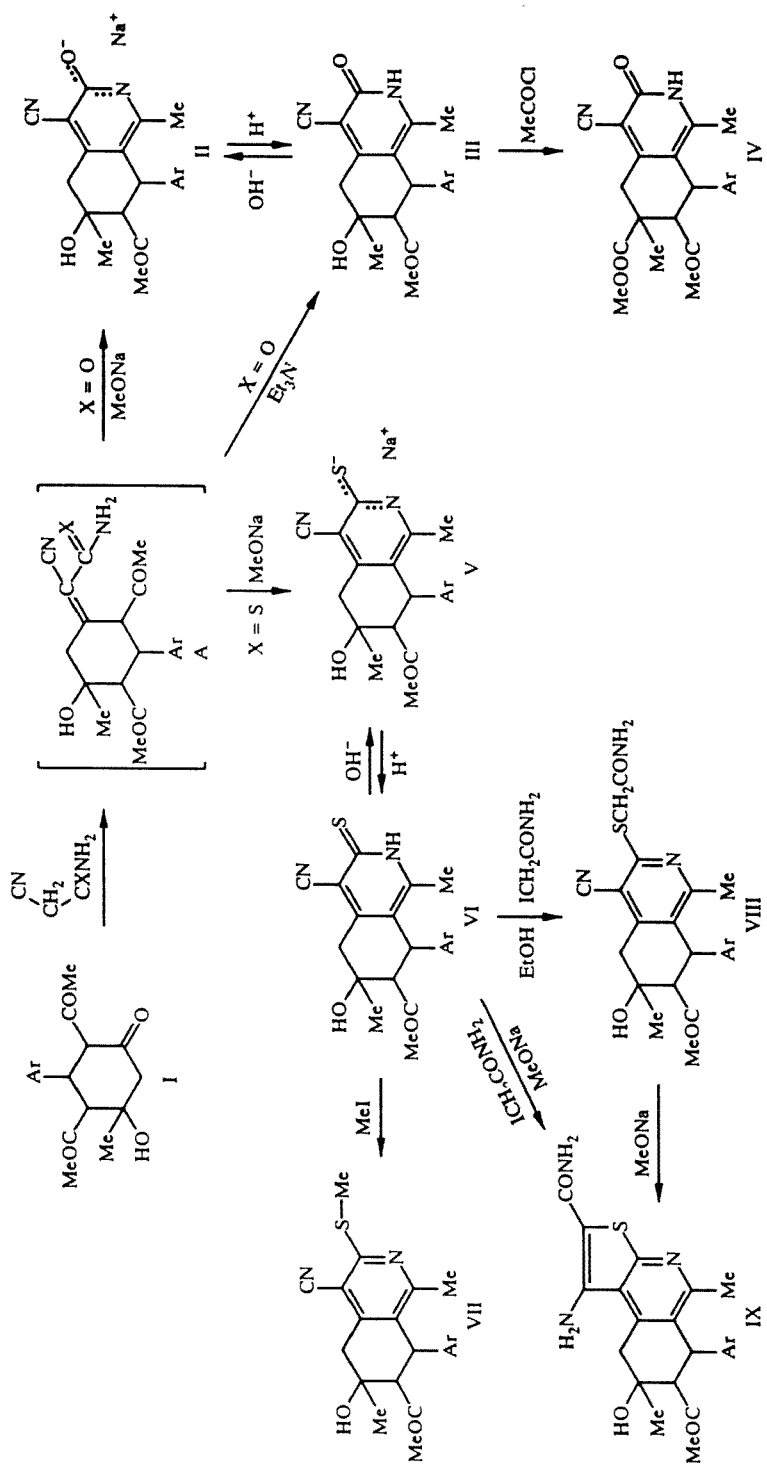
We synthesized and investigated the chemical properties of 3,6,7,8-tetrahydro-3(2H)-isoquinolinethiones containing acetyl and hydroxy groups. 2,4-Diacetyl-3-aryl-5-methyl-5-hydroxycyclohexan-1-ones (I) were used for this purpose, prepared by the reaction of acetylacetone with unsubstituted, *p*-Cl-, and *p*-CH<sub>3</sub>-substituted benzaldehydes in basic medium [2-4].

In condensation of cyclohexan-1-ones with cyanoacetamide in absolute ethanol in the presence of an equimolar amount of sodium methylate, 8-aryl-7-acetyl-1,6-dimethyl-6-hydroxy-4-cyano-5,6,7,8-tetrahydro-3(2H)-isoquinoline sodium salts II were obtained.

Salts II were dissolved in water and on acidification of the aqueous solution to pH 2, 8-aryl-7-acetyl-1,6-dimethyl-6-hydroxy-4-cyano-5,6,7,8-tetrahydro-3(2H)-isoquinolinones (III) formed. The reverse transformation from compounds III to corresponding sodium salts II took place in ethanol in the presence of sodium hydroxide. Isoquinolinones III were also obtained in condensation of cyclohexanone I with cyanoacetamide in the presence of triethylamine.

We will hypothesize that the reaction takes place in the sequence: in the conditions of the Knoevenagel reaction, the cyanoacetamide anion formed reacts with the endocyclic carbonyl group of cyclohexanone I with formation of product of addition A, in which intramolecular condensation of the NH<sub>2</sub> amide group with the carbonyl of the vicinal exocyclic acetyl group takes place in basic medium with separation of a molecule of water and closing of the pyridine ring.

The PMR spectra of isoquinolinones III (Table 1) are in agreement with the spectra of unsubstituted 5,6,7,8-tetrahydro-3(2H)-isoquinolinones [1, 5]. The PMR spectra of isoquinolinones III contains a signal of NH protons at 12.2-12.5 ppm which is not present in the spectra of sodium salts II. The signals of hydroxyl groups observed in the 4.5-5.0 ppm region disappear on addition of D<sub>2</sub>O. At the same time, the PMR spectrum of the isoquinolinones differs little from the PMR spectra of quinolinones [6]. The <sup>13</sup>C spectrum was taken to definitively confirm the isoquinoline structure of compound IIIa. The chemical shifts for 1-C and 4-C of 117.59 and 98.84 ppm respectively confirm the isoquinolinone structure [7].



I-IX a Ar = Ph, b Ar =  $\text{C}_6\text{H}_4$ -p-Me, c Ar =  $\text{C}_6\text{H}_4$ -p-Cl

TABLE 1. Parameters of the PMR Spectra of Compounds II-IX

| Com-<br>pound | Chemical shifts of protons, $\delta$ , ppm (in DMSO) |                            |                            |                               |              |              |             |             |                  |                  |   | Chemical shifts of protons         |  |  |
|---------------|--|----------------------------|----------------------------|-------------------------------|--------------|--------------|-------------|-------------|------------------|------------------|---|------------------------------------|--|--|
|               | 6-CH <sub>3</sub><br>s, 3H                           | 1-CH <sub>3</sub><br>s, 3H | 7-CH <sub>3</sub><br>s, 3H | 5-CH <sub>3</sub><br>d.d., 2H | 8-H d,<br>1H | 7-H<br>d, 1H | NH<br>s, 1H | OH<br>s, 1H | SSCC, Hz         |                  | 8-Ar                                      | Other protons                      |  |  |
|               |  |                            |                            |                               |              |              |             |             | J <sub>5,5</sub> | J <sub>7,8</sub> |   |                                    |  |  |
| I             | 2  | 3                          | 4                          | 5                             | 6            | 7            | 8           | 9           | 10               | 11               | 12  | 13                                 |  |  |
| IIa           | 1,15   | 1,55                       | 2,05                       | 2,65, 2,80                    | 4,20         | 2,60         | —           | 4,50        | 18,2             | 11,0             | 7,18...7,30 (m, 5H)                       |                                    |  |  |
| IIb           | 1,20   | 1,60                       | 2,10                       | 2,65, 2,80                    | 4,20         | 2,60         | —           | 4,55        | 18,8             | 10,6             | 6,85, 7,10 (d and d, 4H),<br>2,20 (s, 3H) |                                    |  |  |
| IIc           | 1,15   | 1,60                       | 2,10                       | 2,65, 2,80                    | 4,20         | 2,60         | —           | 4,50        | 18,2             | 10,2             | 6,85, 7,20 (d and d, 4H)                  |                                    |  |  |
| IIIa          | 1,20   | 1,65                       | 2,05                       | 2,70, 3,05                    | 4,25         | 2,80         | 12,20       | 4,80        | 18,2             | 11,0             | 6,80...7,20 (m, 5H)                       |                                    |  |  |
| IIIb          | 1,20   | 1,70                       | 2,10                       | 2,70, 3,10                    | 4,20         | 2,70         | 12,15       | 4,80        | 18,8             | 10,6             | 6,80, 7,20 (d and d, 4H),<br>2,15 (s, 3H) |                                    |  |  |
| IIIc          | 1,20   | 1,70                       | 2,10                       | 2,75, 3,10                    | 4,30         | 2,70         | 12,15       | 4,80        | 18,2             | 10,2             | 7,10, 7,25 (d and d, 4H)                  |                                    |  |  |
| IVa           | 1,55   | 1,80                       | 2,10                       | 3,30, 3,95                    | 4,45         | 3,10         | 12,40       | —           | 18,2             | 10,1             | 6,70...7,25 (m, 5H)                       | 1,90 (s, 3H, 7-COCH <sub>3</sub> ) |  |  |
| IVb           | 1,60   | 1,70                       | 1,90                       | 2,90, 4,10                    | 4,30         | 2,90         | 11,60       | —           | 18,8             | 10,6             | 6,80, 6,95 (d and d, 4H),<br>2,20 (s, 3H) | 1,80 (s, 3H, 7-COCH <sub>3</sub> ) |  |  |
| IVc           | 1,50   | 1,70                       | 2,10                       | 3,20, 3,85                    | 4,40         | 2,95         | 12,50       | —           | 18,2             | 10,2             | 7,15, 7,30 (d and d, 4H)                  | 1,80 (s, 3H, 7-COCH <sub>3</sub> ) |  |  |
| Va            | 1,20   | 1,70                       | 2,07                       | 2,69, 2,97                    | 4,31         | 2,78         | —           | 4,64        | 17,6             | 10,5             | 6,90...7,25 (m, 5H)                       |                                    |  |  |
| Vb            | 1,10   | 1,65                       | 2,00                       | 2,60, 2,87                    | 4,15         | 2,70         | —           | 4,65        | 17,5             | 10,0             | 6,70, 6,90 (d and d, 4H),<br>2,15 (s, 3H) |                                    |  |  |
| Vc            | 1,20   | 1,72                       | 2,11                       | 2,69, 2,97                    | 4,34         | 2,74         | —           | 4,70        | 17,6             | 10,3             | 6,90, 7,20 (d and d, 4H)                  |                                    |  |  |
| VIa           | 1,25   | 1,86                       | 2,09                       | 2,85, 3,04                    | 4,41         | 2,89         | 13,65       | 4,91        | 15,7             | 10,3             | 6,70...7,25 (m, 5H)                       |                                    |  |  |

TABLE 1 (continued)

| 1     | 2    | 3    | 4    | 5          | 6    | 7    | 8     | 9    | 10   | 11   | 12  | 13   |
|-------|------|------|------|------------|------|------|-------|------|------|------|---|--|
| VIIb  | 1,12 | 1,67 | 2,02 | 2,69, 2,97 | 4,40 | 2,65 | 13,80 | 4,70 | 16,5 | 10,1 | 6,70, 6,90 (d and d, 4H),<br>2,15 (s, 3H) |  |
| VIIc  | 1,26 | 1,89 | 2,13 | 2,84, 3,03 | 4,45 | 2,87 | 13,79 | 4,96 | 16,4 | 10,4 | 7,10, 7,30 (d and d, 4H)                  |  |
| VIIIa | 1,27 | 1,98 | 2,11 | 2,80, 3,20 | 4,50 | 2,90 | —     | 4,82 | 18,4 | 11,6 | 6,80...7,30 (m, 5H)                       | 2,55 (s, 3H, SCH <sub>3</sub> )  |
| VIIIb | 1,25 | 1,90 | 2,10 | 2,75, 3,20 | 4,45 | 2,75 | —     | 4,75 | 17,2 | 11,6 | 6,85, 7,05 (d and d, 4H),<br>2,20 (s, 3H) | 2,50 (s, 3H, SCH <sub>3</sub> )  |
| VIIIc | 1,27 | 1,99 | 2,12 | 2,80, 3,20 | 4,50 | 2,90 | —     | 4,82 | 17,5 | 10,0 | 6,95, 7,20 (d and d, 4H)                  | 2,53 (s, 3H, SCH <sub>3</sub> )  |
| VIIIa | 1,25 | 1,90 | 2,05 | 2,80, 3,20 | 4,45 | 2,90 | —     | 4,75 | 18,8 | 10,2 | 6,80...7,25 (m, 5H)                       | 3,80 (s, 2H, SCH <sub>2</sub> ), 7,0,<br>7,5 (d, 2H, CONH <sub>2</sub> ) |
| VIIIb | 1,20 | 1,85 | 2,05 | 2,80, 3,30 | 4,40 | 2,80 | —     | 4,75 | 18,2 | 11,0 | 6,80, 7,00 (d and d, 4H),<br>2,15 (s, 3H) | 3,80 (s, 2H, SCH <sub>2</sub> ), 7,0,<br>7,5 (d, 2H, CONH <sub>2</sub> ) |
| VIIIc | 1,20 | 1,90 | 2,05 | 2,80, 3,20 | 4,50 | 2,80 | —     | 4,80 | 18,8 | 10,6 | 6,90, 7,22 (d and d, 1H)                  | 3,80 (s, 2H, SCH <sub>2</sub> ), 6,9,<br>7,4 (d, 2H, CONH <sub>2</sub> ) |
| IXa   | 1,25 | 1,90 | 2,05 | 2,65, 2,80 | 4,20 | 2,60 | —     | 4,50 | 18,8 | 10,2 | 7,10...7,30 (m, 5H)                       | 6,70...7,20 (m, 4H,<br>1-NH <sub>2</sub> , 2-CONH <sub>2</sub> )         |
| IXb   | 1,25 | 2,00 | 2,10 | 2,65, 2,80 | 4,20 | 2,60 | —     | 4,55 | 18,8 | 10,4 | 6,85, 7,20 (d and d, 4H),<br>2,20 (s, 3H) | 6,70...7,20 (m, 4H,<br>1-NH <sub>2</sub> , 2-CONH <sub>2</sub> )         |
| IXc   | 1,35 | 2,00 | 2,05 | 2,65, 2,80 | 4,20 | 2,60 | —     | 4,51 | 18,6 | 10,4 | 6,85, 7,20 (d and d, 4H)                  | 6,70...7,20 (m, 4H,<br>1-NH <sub>2</sub> , 2-CONH <sub>2</sub> )         |

TABLE 2. Characteristics of Synthesized Compounds II-IX

| Com-<br>pound | Empirical<br>formula  | mp,<br>°C | UV spectrum, $\lambda_{\max}$<br>nm (log $\epsilon$ ) | IR spectrum, $\text{cm}^{-1}$ |      |                          |     | Yield,<br>% |
|---------------|---|-----------|---|-------------------------------|------|--------------------------|-----|-------------|
|               |   |           |   | CO                            | CN   | NH, NH <sub>2</sub> , OH |     |             |
| IIa           | $\text{C}_{30}\text{H}_{19}\text{O}_3\text{N}_2\text{Na}$   | 226...227 | 342 (8,6), 220 (3,6)                                  | 1744                          | 2225 | 3320                     | 64  |             |
| IIb           | $\text{C}_{21}\text{H}_{21}\text{O}_3\text{N}_2\text{Na}$   | 217...218 | 344 (7,2), 220 (3,9)                                  | 1745                          | 2225 | 3300                     | 97  |             |
| IIc           | $\text{C}_{30}\text{H}_{18}\text{O}_3\text{N}_2\text{ClNa}$ | 264...266 | 348 (9,1), 222 (3,1)                                  | 1740                          | 2225 | 3440                     | 52  |             |
| IIIa          | $\text{C}_{20}\text{H}_{20}\text{O}_3\text{N}_2$            | 247...264 | 342 (9,0), 220 (3,3)                                  | 1740                          | 2225 | 3470                     | 90* |             |
| IIIb          | $\text{C}_{31}\text{H}_{22}\text{O}_3\text{N}_2$            | 267...268 | 346 (9,1), 222 (3,4)                                  | 1745                          | 2225 | 3420                     | 95* |             |
| IIIc          | $\text{C}_{20}\text{H}_{19}\text{O}_3\text{N}_2\text{Cl}$   | 263...264 | 346 (8,7), 222 (3,0)                                  | 1750                          | 2225 | 3450                     | 91* |             |
| IVa           | $\text{C}_{22}\text{H}_{22}\text{O}_4\text{N}_2$            | 233...234 | 335 (8,1), 215 (10,2)                                 | 1735; 1660                    | 2225 | 3480                     | 40  |             |
| IVb           | $\text{C}_{23}\text{H}_{24}\text{O}_4\text{N}_2$            | 235...236 | 340 (8,4), 213 (11,0)                                 | 1740; 1660                    | 2225 | 3490                     | 70  |             |
| IVc           | $\text{C}_{22}\text{H}_{21}\text{O}_4\text{N}_2\text{Cl}$   | 225...226 | 337 (8,7), 210 (10,5)                                 | 1740; 1660                    | 2225 | 3480                     | 65  |             |
| Va            | $\text{C}_{20}\text{H}_{19}\text{O}_2\text{N}_2\text{Na}$   | 249...250 | 210 (9,2), 312 (4,5), 400 (1,9)                       | 1710                          | 2225 | 3450                     | 84  |             |
| Vb            | $\text{C}_{21}\text{H}_{21}\text{O}_2\text{N}_2\text{Na}$   | 247...248 | 212 (9,1), 314 (4,1), 400 (2,1)                       | 1700                          | 2225 | 3440                     | 86  |             |
| Vc            | $\text{C}_{21}\text{H}_{21}\text{O}_2\text{N}_2\text{SNa}$  | 285...286 | 212 (9,1), 315 (4,5), 400 (2,2)                       | 1710                          | 2225 | 3450                     | 89  |             |
| VIa           | $\text{C}_{20}\text{H}_{18}\text{O}_2\text{N}_2\text{ClNa}$ | 269...270 | 210 (8,7), 312 (4,6), 400 (1,9)                       | 1710                          | 2225 | 3500                     | 79† |             |
| VIb           | $\text{C}_{20}\text{H}_{20}\text{O}_2\text{N}_2\text{S}$    | 246...247 | 212 (8,9), 314 (4,1), 400 (2,3)                       | 1710                          | 2220 | 3400                     | 91† |             |
| VIIa          | $\text{C}_{21}\text{H}_{22}\text{O}_2\text{N}_2\text{S}$    | 252...253 | 213 (8,8), 313 (4,2), 400 (2,2)                       | 1710                          | 2220 | 3430                     | 88† |             |
| VIIb          | $\text{C}_{20}\text{H}_{19}\text{O}_2\text{N}_2\text{Cl}$   | 200...201 | 210 (8,6), 270 (8,7), 316 (4,6)                       | 1710                          | 2225 | 3500                     | 81  |             |
| VIIc          | $\text{C}_{21}\text{H}_{22}\text{O}_2\text{N}_2\text{S}$    | 192...193 | 210 (8,3), 272 (8,4), 314 (4,3)                       | 1710                          | 2225 | 3420                     | 52  |             |
| VIIIa         | $\text{C}_{21}\text{H}_{21}\text{O}_2\text{N}_2\text{Cl}$   | 202...203 | 210 (8,0), 270 (8,9), 311 (4,4)                       | 1710                          | 2225 | 3470                     | 49  |             |
| VIIIb         | $\text{C}_{22}\text{H}_{23}\text{O}_3\text{N}_3\text{S}$    | 223...224 | 225 (9,9), 268 (9,2), 307 (3,4)                       | 1710                          | 2220 | 3380                     | 55  |             |
| VIIIc         | $\text{C}_{23}\text{H}_{25}\text{O}_3\text{N}_3\text{S}$    | 235...236 | 210 (9,9), 268 (9,7), 305 (3,5)                       | 1710                          | 2220 | 3360                     | 63  |             |
| IXa           | $\text{C}_{22}\text{H}_{22}\text{O}_3\text{N}_3\text{Cl}$   | 187...188 | 210 (9,8), 268 (9,4), 305 (3,7)                       | 1710                          | 2220 | 3200; 3420               | 51  |             |
| IXb           | $\text{C}_{22}\text{H}_{23}\text{O}_3\text{N}_3\text{S}$    | 298...299 | 215 (9,7), 282 (9,8), 350 (4,2)                       | 1710                          | 2220 | 3200; 3425               | 45* |             |
| IXc           | $\text{C}_{23}\text{H}_{25}\text{O}_3\text{N}_3\text{S}$    | 248...250 | 210 (9,6), 282 (9,7), 350 (4,4)                       | 1710                          | 2220 | 3200; 3460               | 52* |             |
| IXc           | $\text{C}_{22}\text{H}_{22}\text{O}_3\text{N}_3\text{Cl}$   | 263...264 | 210 (9,8), 282 (9,9), 350 (4,5)                       | 1710                          | 2220 | 3200; 3450               | 41* |             |

\*Method B.

†Method A.

The absorption band of medium intensity at  $3400\text{ cm}^{-1}$  in the IR spectra of isoquinolinones II and III (Table 2) indicates an associated OH group.

Acylation of sodium salt II with acetyl chloride yielded 7-acetyl-6-acetyloxy-1,6-dimethyl-8-aryl-4-cyano-5,6,7,8-tetrahydro-3(2H)-isoquinolinones IV. Splitting of the hydroxyl group at the 6-C atom in the form of a molecule of water (with separation of a vicinal proton) is not observed in these conditions and acylation takes place.

In contrast to the spectra of salt II, there are no signals from the OH group proton in the PMR spectra of compounds IV, and signals of NH groups at 11.6-12.5 ppm and the signal of a third methyl group at 1.8-1.9 ppm for the acetyloxy group at 6-C appear again.

8-Aryl-7-acetyl-1,6-dimethyl-6-hydroxy-4-cyano-3,6,7,8-tetrahydro-3(2H)-isoquinolinethiones V are formed in condensation of cyclohexanone I with cyanothioacetamide; similar to the oxygen containing derivatives, they are transformed into the corresponding 8-aryl-7-acetyl-1,6-dimethyl-6-hydroxy-4-cyano-5,6,7,8-tetrahydro-3(2H)isoquinolinethiones VI in acid medium.

The PMR spectra of derivatives of isoquinolinethiones VI and their sodium salts V do not significantly differ from the spectra of isoquinolinones II and III (Table 1). The sulfur atom in isoquinolinethione VI, in comparison to the oxygen atom in isoquinolinone III, deshields the signal of the nitrogen hydrogen proton by 1.5 ppm on average. A decrease in  $^2J_{5,5}$  is also observed (Table 1).

Studies of the chemical properties of isoquinolinethiones V showed that these compounds are easily alkylated and can be used for synthesis of new heterocyclic systems.

5,6,7,8-Tetrahydro-3(2H)-isoquinolinethiones VI are alkylated by methyl iodide and iodoacetamide with formation of 8-aryl-7-acetyl-1,6-dimethyl-3-methylthio-6-hydroxy-4-cyano-5,6,7,8-tetrahydro-3-isoquinolines VII and 8-aryl-3-carbamoylmethylthio-1,6-dimethyl-6-hydroxy-4-cyano-5,6,7,8-tetrahydro-3-isoquinolines VIII, respectively.

There is no signal of the NH proton in the PMR spectra of alkylated compounds VIII and VIII and signals characteristic of the protons in S-CH<sub>3</sub>, S-CH<sub>2</sub>, and CONH<sub>2</sub> groups, respectively appear (Table 1). Although the UV spectra of isoquinolinethiones V and VI have an absorption band at 400 nm, a hypsochromic shift to 305-316 nm is observed in the case of compounds VII and VIII. Isoquinolines VIII in basic medium are cyclized according to Thorpe with formation of 1-amino-6-aryl-7-acetyl-2-carbamoyl-5,8-dimethyl-8-hydroxy-6,7,8,9-tetrahydrothiophene[2,3-c]isoquinoline (IX).

There are no bands of the CN group in the IR spectra of thiophene[2,3-c]isoquinoline IX and no signals from S-CH<sub>2</sub> group protons in the PMR spectra. Due to growth of the conjugated chain in thiophene[2,3-c]isoquinoline IX, the long-wave maximum in the UV spectra is shifted bathochromically to 350 nm in comparison to isoquinolines VII, for which there is a long-wave maximum in the 305-307 nm region.

## EXPERIMENTAL

The IR spectra were recorded on a Perkin-Elmer 580B (in petrolatum) and the UV spectra were recorded on a Specord UV-vis spectrometer (in ethanol). The <sup>1</sup>H and <sup>13</sup>C PMR spectra were made on WH-90/DS and WH-360 spectrometers. The internal standard was tetramethylsilane. The basic characteristics of the synthesized compounds are reported in Tables 1-2.

The data from elemental analysis of the compounds for C, H, N, and S correspond to the calculated data.

2,4-Diacetyl-5-methyl-5-hydroxy-3-arylcyclohexanones (Ia-c) were prepared similarly to the published data [3].

**7-Acetyl-1,6-dimethyl-6-hydroxy-8-phenyl-4-cyano-5,6,7,8-tetrahydro-3(2H)-isoquinolinone Sodium Salt (IIa).** A solution of 0.4 g (4.8 mmole) of cyanoacetamide in 40 ml of ethanol was added to a solution of 1.0 g (3.5 mmole) of Ia in 40 ml of ethanol. It was heated to 70°C and 3 ml of 7% (3.9 mmole) sodium methylate was added. After cooling to -5°C, the sediment of IIa was filtered off. It was recrystallized from ethanol. Yield of 0.82 g (65%).

Compounds IIb, c were prepared similarly to IIa.

**7-Acetyl-1,6-dimethyl-6-hydroxy-8-phenyl-4-cyano-5,6,7,8-tetrahydro-3(2H)-isoquinolinone (IIIa).** A. A solution of 0.4 g (4.8 mmole) of cyanoacetamide in 40 ml of ethanol and 3 ml of triethylamine was added to a solution of 1.0 g (3.5 mmole) of Ia in 40 ml of ethanol. The mixture was heated at 70°C for 2 h, evaporated to 30 ml, cooled, and left at -5°C for 20 h. The sediment of IIIa was filtered off and recrystallized from ethanol. Yield of 0.75 g (64%).

B. Here 1.0 g (2.8 mmole) of IIa was dissolved in 150 ml of water and acidified to pH 2 with hydrochloric acid. The sediment of IIIa was filtered off and recrystallized from ethanol. Yield of 0.85 g (90%). <sup>13</sup>C NMR spectrum (DMSO-D<sub>6</sub>): 19.66 (1-CH<sub>3</sub>), 27.57 (6-CH<sub>3</sub>), 34.49 (CH<sub>3</sub>CO), 42.57 (5-C), 44.40 (8-C), 62.87 (7-C), 68.86 (6-C), 98.84 (4-C), 115.52 (CN), 117.19 (1-C), 126.75, 127.75, 129.15, 148.00 (C<sub>6</sub>H<sub>5</sub>), 151.01, 158.21 (9,10-D); 162.38 (3-C), 215.65 (CH<sub>3</sub>CO).

Compounds IIIb, c were prepared similarly to IIIa with method A.

**7-Acetyl-1,6-acetyloxy-1,6-dimethyl-8-phenyl-4-cyano-5,6,7,8-tetrahydro-3(2H)-isoquinolinone (IVa).** Here 0.5 g (1.4 mmole) of IIa was suspended in 20 ml of acetyl chloride and boiled for 1 h. The reaction mixture was poured on ice, and the sediment of IVa was filtered off and recrystallized from ethanol. Yield of 0.2 g (40%).

Compounds IVb, c were prepared similarly to IVa.

**7-Acetyl-1,6-dimethyl-6-hydroxy-8-phenyl-4-cyano-5,6,7,8-tetrahydro-3(2H)-isoquinolinethione Sodium Salt (Va).** Here 1.0 g (3.5 mmole) of Ia was dissolved in 40 ml of ethanol and a solution of 0.4 g (4.0 mmole) of cyanothioacetamide in 40 ml of ethanol was added. The mixture was heated to 75°C and 3 ml of 7% (3.9 mmole) sodium methylate was added. The sediment of Va was cooled and filtered off. It was washed five times with ethanol. Yield of 1.1 g (84%).

Compounds Vb, c were prepared similarly to Va.

**7-Acetyl-1,6-dimethyl-6-hydroxy-8-phenyl-4-cyano-5,6,7,8-tetrahydro-3(2H)-isoquinolinethione (VIa).** A. Here 1.0 g (2.7 mmole) of Va was dissolved in 200 ml of water and acidified with hydrochloric acid to pH 2. The sediment of VIa was filtered off and recrystallized from ethanol. Yield of 0.74 g (79%).

B. A solution of 0.4 g (4.0 mmole) of cyanothioacetamide in 40 ml of ethanol and 3 ml of triethylamine were added to a solution of 1.0 g (3.5 mmole) of Va in 40 ml of ethanol. The mixture was heated at 70°C for 2 h. After evaporation to 30 ml, it was left at -5°C for 20 h. The sediment was filtered off and recrystallized from ethanol. Yield of 0.58 g (62%).

Compounds VIb, c were prepared similarly to VIa with method A.

**7-Acetyl-1,6-dimethyl-3-methylthio-6-hydroxy-8-phenyl-4-cyano-5,6,7,8-tetrahydro-3(2H)-isoquinoline (VIIa).** Here 0.6 g (1.6 mmole) of Va was suspended in 15 ml of ethanol and 10 ml of methyl iodide was added and heated at 70°C until totally dissolved. After evaporation to 4 ml, the residue of VIIa was filtered off and recrystallized from methanol. Yield of 0.48 g (81%).

Compounds VIIb, c were obtained similarly to VIIa.

**7-Acetyl-3-carbamoylmethylthio-1,6-dimethyl-6-hydroxy-8-phenyl-4-cyano-5,6,7,8-tetrahydro-3(2H)-isoquinoline (VIIIa).** Here 0.5 g (1.3 mmole) of Va was suspended in 25 ml of ethanol and a solution of 0.4 g (2.2 mmole) of iodoacetamide in 10 ml of ethanol was added and heated at 70°C until totally dissolved. The mixture was cooled to 20°C and 20 ml of water was added by drops. It was left at -5°C for 20 h. The sediment of VIIIa was filtered off and recrystallized from methanol. Yield of 0.4 g (81%).

Compounds VIIIb, c were prepared similarly to VIIIa.

**1-Amino-7-acetyl-2-carbamoyl-5,8-dimethyl-8-hydroxy-6-phenyl-6,7,8,9-tetrahydrothiophene[2,3-c]isoquinoline (IXa).** A. Here 0.5 g (1.3 mmole) of Va was suspended in 25 ml of ethanol and a solution of 0.4 g (2.2 mmole) of iodoacetamide in 10 ml of ethanol was added. It was stirred at 70°C until totally dissolved. The mixture was cooled to 50°C, 3 ml of 7% (3.9 mmole) sodium methylate was added, and it was left at room temperature for 12 h. The sediment of IXa was filtered off and recrystallized from ethanol. Yield of 0.23 g (45%).

B. Here 0.5 g (1.3 mmole) of VIIIa was dissolved in 25 ml of ethanol and 15 ml (1.8 mmole) of 7% sodium methylate was added. It was left for 12 h at room temperature. The mixture was cooled and the sediment of IXa was filtered off and recrystallized from ethanol. Yield of 0.4 g (80%).

Compounds IXb, c were prepared similarly to compound IXa.

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