water, and extracted with dichloroethane and the extracts were dried with anhydrous sodium sulfate. After the elimination of the solvent, the residue was distilled in vacuum. Compounds VII and X were obtained similarly. Diallyl pyridine-2,5-dicarboxylate was obtained by the same method, mp 54° C (from ethanol); according to the literature [4], mp 53° C.

Dipropargyl pyridine-2,4-dicarboxylate (III). In drops, 25 ml of propargyl alcohol was added to the chloride of pyridine-2,4-dicarboxylic acid obtained from 10 g (0.06 mole) of the diacid. The reaction mixture was boiled in the water bath for 4–5 hr, and then the excess of propargyl alcohol was distilled off in vacuum. The residual oil was triturated with ether and recrystallized. Compounds V and X were obtained similarly. In the synthesis of VIII, after being boiled the reaction mixture was treated with saturated sodium carbonate solution and the precipitate was filtered off and recrystallized.

Attempts to obtain the divinyl, diallyl, and dipropargyl esters of pyridine-2,3-dicarboxylic acid were unsuccessful.

REFERENCES

1. A. M. Sladkov, V. V. Korshak, and A. G. Maksumov, Izv. AN SSSR, OKhN, 1343, 1963.

2. V. V. Korshak, A. M. Sladkov, and A. G. Maksumov, Uzb. khim. zh., 1, 67, 1964.

3. N. D. Negodyaev and Z. V. Pushkareva, KhGS [Chemistry of Heterocyclic Compounds], 2, 586, 1966.

4. B. F. Ustavshchikov and T. R. Titova, Uch. zap. Yaroslavsk. tekhnol. inst., 5, 1961.

5. A. N. Nesmeyanov, I. F. Lutsenko, and R. M. Khomutov, Izv. AN SSSR, OKhN, 942, 1957.

28 February 1967

Kirov Ural Polytechnic Institute, Sverdlovsk

N-SUBSTITUTED 2,5-DIMETHYL-4-ETHYNYL(VINYL)PIPERID-4-OLS

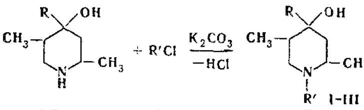
A. Sh. Sharifkanov, K. Kh. Tokmurzin, and R. B. Atshabarova

Khimiya Geterotsiklicheskikh Soedinenii, Vol. 5, No. 4, pp. 746–747, 1969

UDC 547.827

The γ-isomers of 1-(3-chlorobuten-2-yl)- and 1-benzyl-2,5-dimethyl-4-ethynylpiperid-4-ols (I, II) and of 1-(3-chlorobuten-2-yl)-2,5-diemethyl-4-vinylpiperid-4-ol (III) and the quaternary salts of compounds I–III and of the β-isomers of the 1,2,5-trimethyl-4-ethynyl(vinyl)piperid-4-ols [1] have been synthesized.

1-Alkenyl-4-ethynyl(vinyl)-2,5-dimethylpiperid-4-ols have been synthesized previously [2–4] and have been used to obtain various esters. Continuing systematic investigations on the synthesis of new physiologically active compounds from 2,5-dimethylpiperid-4-one [5] we have synthesized the γ-isomers of 1-(3-chloro-buten-2-yl)- and 1-benzyl-4a-ethynyl-2e,5e-dimethylpiperid-4e-ols (I, II) and of 1-(3-chlorobuten-2-yl)-2e,5e-dimethyl-4a-vinylpiperid-4e-ol (III) by the reaction of the individual γ-isomers of 4-ethynyl(vinyl)-2,5-dimethylpiperid-4-ols with the corresponding halogen derivatives in absolute butanol in the presence of anhydrous potassium carbonate [8].



I-III

I $R = -C{\equiv}CH$, $R' = -CH_2CH{=}CClCH_3$;
II $R = -C{\equiv}CH$, $R' = -CH_2C_6H_5$;
III $R = -CH{=}CH_2$, $R' = -CH_2CH{=}CClCH_3$

EXPERIMENTAL

1-(3-Chlorobuten-2-yl)-4-ethynyl-2,5-dimethylpiperid-4-ol (I). With vigorous stirring, a solution of 9 g (0.072 mole) of 1,3-dichlorobut-2-ene in 20 ml of absolute butanol was added dropwise to a mixture of 10 g (0.065 mole) of the γ-isomer of 4-ethynyl-2,5-dimethylpiperid-4-ol (IV) and 18 g of powdered anhydrous potassium carbonate in 50 ml of absolute butanol, and the mixture was heated at 80–85° C for 7 hr. On the following day, the precipitate of salts was filtered off and washed, the butanol was distilled off in vacuum, and the residue was crystallized from absolute benzene, giving 10.8 g (68%) of I, mp 98–99° C. Found, %: N 5.77, 5.89. Calculated for $C_{13}H_{20}ClNO$, %: N 5.79. The hydrochloride of the piperidol I was obtained by the addition of an ethereal solution of dry hydrogen chloride to an ethereal solution of I. Yield 77%, mp 214–215° C (from ethanol with the addition of acetone). Found, %: Cl 12.76, 12.39; N 5.04, 4.93. Calculated for $C_{13}H_{20}ClNO \cdot HCl$, %: Cl 12.76; N 5.04.

The methiodide of the piperidol I was obtained by heating a mixture of 1.5 g (0.006 mole) of the piperidol and 0.96 g (0.006 mole) of methyl iodide in 20 ml of absolute benzene at 75–80° C for 2 hr. Yield 0.47 g (20%), mp 158–160° C (from acetone). Found, %: N 3.53, 3.55. Calculated for $C_{14}H_{23}ClINO$, %: N 3.65. The methiodides of II and III were obtained similarly.

1-Benzyl-4-ethynyl-2,5-dimethylpiperid-4-ol (II) was obtained in a similar manner to I from IV and benzyl chloride. Yield of II 74%, mp 60–61° C (from gasoline). Found, %: C 78.79; H 8.90, 8.81; N 6.08, 6.11. Calculated for $C_{16}H_{21}NO$, %: C 79.01; H 8.64; N 5.76%. Hydrochloride of the piperidol II, mp 238–239° C (from ethanol). Found, %: Cl 12.70, 12.77; N 5.27, 5.29. Calculated for $C_{16}H_{21}NO \cdot HCl$, %: Cl 12.70; N 5.01.

The methiodide of the piperidol II, yield 56%, mp 116–117° C (from acetone). Found, %: N 3.71, 3.83. Calculated for $C_{17}H_{24}INO$, %: N 3.64.

1-(3-Chlorobuten-2-yl)-2,5-dimethyl-4-vinylpiperid-4-ol (III) was obtained from the γ-isomer of 2,5-dimethyl-4-vinylpiperid-4-ol in a similar manner to I. Yield 71%, mp 82–83° C (from gasoline). Found, %: N 5.60, 5.45. Calculated for $C_{13}H_{22}ClNO$, %: N 5.75. Hydrochloride of III, mp 215–216° C. Found, %: Cl 12.41, 12.30; N 5.27, 5.18. Calculated for $C_{13}H_{22}ClNO \cdot HCl$, %: Cl 12.64; N 5.00. The methiodide of the piperidol III, yield 37%, mp 161–

162° C (from acetone). Found, %: N 3.30, 3.32. Calculated for $C_{14}H_{25}ClINO$, %: N 3.63.

Allyl bromide derivative of 4-ethynyl-1, 2, 5-trimethylpiperid-4-ol. A mixture of 2 g of the β-isomer of 4-ethynyl-1, 2, 5-trimethylpiperid-4-ol [1] and 1.6 g of allyl bromide in 10 ml of absolute benzene was heated at 95–100° C for 7.5 hr. The precipitate was separated off and crystallized from ethanol, giving 2.2 g (61%) of the allyl bromide derivative, mp 204–205° C. Found, %: C 54.42; H 8.38; Br 28.40; N 5.10. Calculated for $C_{13}H_{22}BrNO$, %: C 54.17; H 7.69; Br 27.74; N 4.85.

The allyl bromide derivative of the β-isomer of 1, 2, 5-trimethyl-4-vinylpiperid-4-ol was obtained in a similar manner to the preceding compound, yield 63%, mp 201–203° C (from ethanol). Found, %: C 54.18; H 8.79; Br 28.32; N 5.03. Calculated for $C_{13}H_{24}BrNO$, %: C 53.80; H 8.34; Br 27.53; N 4.82.

REFERENCES

1. I. N. Nazarov, V. Ya. Raigorodskaya, and V. A. Rudenko, Izv. AN SSSR, OKhN, 504, 1949.
2. I. N. Nazarov and A. Sh. Sharifkanov, Izv. AN SSSR, OKhN, 446, 1958.
3. I. N. Nazarov, A. Sh. Sharifkanov, and T. G. Sarbaev, ZhOKh, 30, 2904, 1960.
4. I. N. Nazarov, A. Sh. Sharifkanov, and S. A. Yusupov, ZhOKh, 30, 3608, 1960.
5. I. N. Nazarov and V. A. Rudenko, Izv. AN SSSR, OKhN, 610, 1948.
6. I. N. Nazarov, A. Sh. Sharifkanov, S. A. Yusupov, and T. G. Sarbaev, ZhOKh, 30, 3267, 1960.
7. A. Sh. Sharifkanov, T. G. Sarbaev, and S. A. Yusupov, ZhOKh, 34, 2571, 1964.
8. I. N. Nazarov, A. Sh. Sharifkanov, and K. F. Danilova, ZhOKh, 27, 1963, 1957.

24 May 1967

Kazakh State University,
Alma-Ata.

INVESTIGATIONS IN THE FIELD OF THE CHEMISTRY OF HETEROCYCLES

XLVI. Synthesis and Biological Activity of Some 2-Aminomethyl-3-arylquinazolones*

Yu. V. Kozhevnikov and P. A. Petyunin

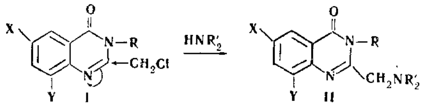
Khimiya Geterotsiklicheskikh Soedinenii, Vol. 5, No. 4, pp. 747–749, 1969

UDC 547.856.1.07:541.69

The reaction of 3-aryl-2-chloromethylquinazol-4-ones with secondary amines has given a number of previously unreported 2-aminomethyl-3-arylquinazol-4-ones, and their biological activity has been studied.

Effective preparations with a broad spectrum of pharmacological activity have been found among the 3-aryl-2-methylquinoxazol-4-ones [2–7]. It appeared of interest to synthesize 3-arylquinazol-4-ones with aminomethyl substituents in position 2 and to subject them to pharmacological study.

As the starting compounds we used 3-aryl-2-chloromethylquinazol-4-ones (I) [8] and also 6-chloro-2-chloromethyl-3-(4'-chlorophenyl)quinazol-4-one (Ia) and 6,8-dichloro-2-chloromethyl-3-(4'-ethoxyphenyl) quinazol-4-one (Ib), obtained as described previously [8] from the 4'-chloroanilide of 5-chloroanthranilic acid (III) and the 4'-phenetidide of 3,5-dichloroanthranilic acid (IV), respectively.



a X = Cl, Y = H, R = 4'-ClC_6H_4; b X = Y = Cl, R = 4'-$C_2H_5OC_6H_4$

The chlorine in the CH_2Cl group of I is activated by the quinazolone ring and, therefore, readily takes part in a nucleophilic substitution reaction. Thus, when compound I was heated with diethylamine, piperidine, and morpholine, the corresponding 2-aminomethyl-3-arylquinazol-4-ones (II) were formed in high yields.

They are colorless crystalline substances which form well-crystalline hydrochlorides and picrates.

The structure of the quinazolone compounds II was confirmed by the UV and IR absorption spectra of Ia, Ib, and V. The UV spectrum of V is characterized by the presence of two maxima at 229 nm (log ε 4.66) and 265 nm (log ε 4.07) (cf. [8]); the IR spectra of Ia, Ib, and V show the following bands: 1690–1688 (CO), 1632–1606, 1595–1565, and 1508–1494 cm^{-1} (these may be assigned provisionally to the vibrations of the quinazolone ring) [9].

The pharmacological tests showed that the quinazolones V–XVIII possesss a tranquillizing and analgesic action; the analgesic activity decreases in the following sequence: VIII > VII > X > XIV > XIII > XVII > XVI*.

---

*For part XLV, see [1].

*The investigations were carried out under the direction of Prof. V. M. Grishina, to whom the authors express their deep gratitude.