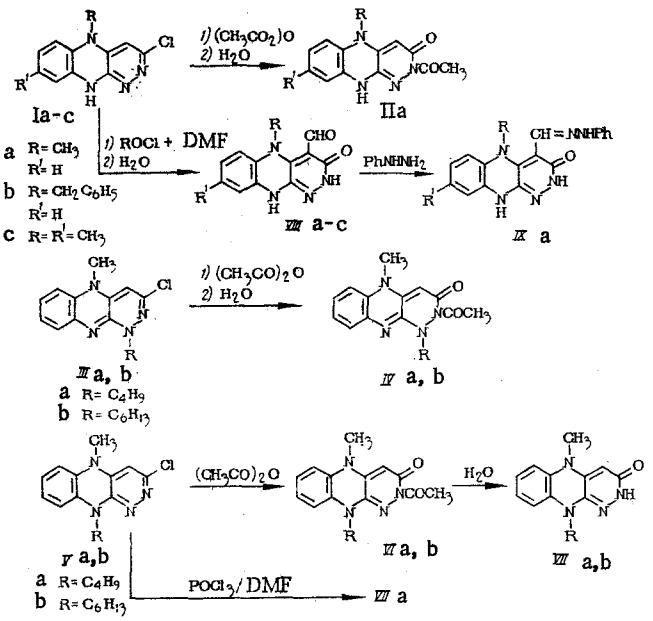
PYRIDAZINOQUINOXALINES.

VIII. CONVERSION OF 3-CHLORHYDROPYRIDAZINO[4,3-b]QUINOXALINES INTO 3-KETO DERIVATIVES

T. V. Kartseva, G. S. Predvoditeleva,
L. I. Lazareva, and V. I. Shvedov

UDC 615.281.221.1:547.863.1].012.1

In continuation of the search for substances possessing bacteriostatic activity among derivatives of dihydropyridazino[4,3-b]quinoxaline [1, 2] it seemed of interest to introduce a keto group into the pyridazine nucleus of this heterocyclic system. The synthesis of such type of compounds is one of the ways of molecular modification for biologically important derivatives of benzopteridine among which are found antimetabolites possessing antivitamin, antibacterial, and antitumor activity [3]. With this aim the synthesis has been effected of, for example, keto derivatives in the pyridazino[4,5-b]quinoxaline series starting from quinoxaline dicarboxylic acid [4]. To obtain similar compounds we started from a preparation of the tricyclic system containing chlorine in the pyridazine ring.



The formation of pyridazine keto derivatives on boiling chloropyridazines with acetic anhydride has been described in the literature [5]. The analogous reaction was observed for chloropyridazines included in a condensed tricyclic system of the diazaphenoxazine type on interaction with acetic anhydride [6] and with Vilsmeier reagent, since the normal products of the Vilsmeier reaction were not detected in the latter case [7].

We have investigated the interaction of substituted 3-chlordihydropyridazino[4,3-b] quinoxalines with acetic anhydride and with the Vilsmeier reagent.

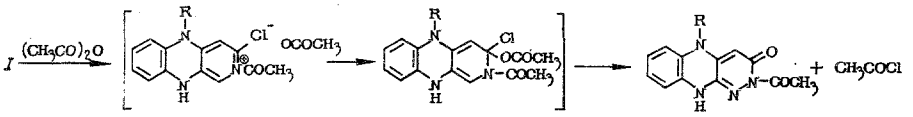
It was shown that on boiling 3-chloro derivatives of (I) and also of their 1- and 10-alkyl substituted derivatives with acetic anhydride, the formation of the corresponding

S. Ordzhonikidze All-Union Scientific-Research Institute for Pharmaceutical Chemistry, Moscow. Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 15, No. 6, pp. 52-55, June, 1981. Original article submitted November 19, 1980.

 0091-150X/81/1506-0400$07.50

keto derivatives occurred. This was confirmed by the appearance in the IR spectra of the compounds obtained (II, IV, and VI) of absorption bands corresponding to a carbonyl group in the 1640 cm^{-1} region and to the amide carbonyl of the N-acetyl group in the 1695-1660 cm^{-1} region.

By analogy with the mechanism proposed previously in [5] for the reaction to prepare pyridazones from chloropyridazines by boiling with acetic anhydride, it is possible to propose the following scheme for the conversion of 3-chloropyridazinoquinoxalines:



which includes the formation of a quaternary salt on the nitrogen atom at position 2, attack by $OCOCH_3$ anion at the carbon at position 3, breaking of the double bond, and splitting off acetyl chloride.

Confirmation of the proposed scheme may be partially afforded by the extremely facile conversion, detected by us previously [2], of 3-chloro-1-alkylpyridazinoquinoxalines quaternized at nitrogen in position 2 into 3-keto-1,2-dialkyl derivatives in the presence of 2% aqueous alkali at room temperature. At the same time the initial compound (I) was not subject to change during many hours boiling with 10% aqueous alkali solution. The acetyl group in the 3-keto derivative (VIa) was hydrolyzed on treatment with water (to compound VIIa). It was shown that the 3-keto derivative obtained from (Ia) and acetic anhydride contained only one acetyl group both after contact of the reaction mass with water and under anhydrous conditions. Proceeding from the fact that (I) is not acetylated under mild conditions and gave the monoacetylderivative (IIa) on boiling with acetic anhydride it should be regarded that the acetyl group is at the 2 position.

Reaction of 3-chloropyridazinoquinoxalines (I) and (V) with Vilsmeier reagent proceeded even at room temperature to the corresponding keto derivative but compound (I) was also subject to the normal process of C formylation. The reaction products were 3-keto-4-formyl-5-methyl(benzyl)-5,10-dihydropyridazino[4,3-b]quinoxalines (VIIIa-c). In the IR spectra of these compounds the stretching vibrations of the carbonyl at position 3 appeared in the 1640-1630 cm^{-1} region and an absorption in the 1660-1650 cm^{-1} region corresponding to the stretching vibration of the formyl group. The absence of a signal for the proton at position 4 from the PMR spectra of (VIII) indicated substitution at this position of the formyl group. This signal did appear in the spectra of starting (I) as a sharp singlet at 6 ppm. Two broadened singlets at low field (at $\delta > 11$ ppm) were assigned to protons of NH groups at positions 2 and 10. The structure of (VIIIa) was confirmed by the formation of it from phenylhydrazone (IXa).

The product from the reaction of (VA) with Vilsmeier reagent was a compound (VIIa) identical with that obtained by interaction of (VA) with acetic anhydride.

It might be proposed that conversion of (I) and (Va) into the keto derivatives (VI) and (VII) under conditions of the Vilsmeier reaction proceeded according to a mechanism analogous to that which takes place on interaction of these compounds with acetic anhydride i.e., through the formation of quaternary salts at the nitrogen atom at position 2.

A comparative chemotherapeutic study of the obtained compounds showed that all the 3-keto derivatives were practically inactive in contrast to the initial 3-chloropyridazinoquinoxalines which possessed high antibacterial activity [1, 2].

EXPERIMENTAL

UV spectra were taken on an EPS-3 spectrophotometer and IR spectra in the crystalline state in form of Nujol mulls on a UR-10 spectrophotometer (DDR).

2-Acetyl-3-keto-5-methyl-5,10-dihydropyridazino[4,3-b]quinoxaline (IIa). Method A. A mixture of (Ia) (1 g: 0.0086 mole), acetic anhydride (20 ml), and pyridine (10 ml) was boiled for 4 h and the reaction mixture was poured into water (100 ml). The precipitated orange solid (IIa) was filtered off. Yield was 0.4 g (43.6%), mp 315-316°C (from 70 % aqueous acetic acid).

Method B. A mixture of (Ia) (1 g: 0.0086 mole), acetic anhydride (20 ml), and pyridine (10 ml) was boiled for 4 h. Pyridine and the excess of acetic anhydride was distilled off and the oily residue was treated with a mixture of absolute alcohol and dry ether. The crystalline solid was filtered off. Compound (IIa) (0.5 g: 54.6%) was obtained having mp 314-316°C (from absolute alcohol). IR spectrum, ν, cm^{-1}: 1645, 1655 (C=O). Found, %: C 60.68; H 4.75; N 21.73. $C_{11}H_{10}N_4O$. Calculated, %: C 60.92; H 4.72; N 21.86.

1-Butyl-2-acetyl-3-keto-5-methyl-1,5-dihydropyridazino[4,3-b]quinoxaline (IVa). A mixture of (IIIa) (5 g: 0.0173 mole) and acetic anhydride (50 ml) was boiled for 3 h. The reaction mixture was poured into water (200 ml). The precipitated solid (IVa) was filtered off and washed with water. Yield was 4 g (73.3%), mp 143-146°C (from alcohol). IR spectrum, ν, cm^{-1}: 1640, 1695 (C=O). Found, %: C 65.32; H 6.43; N 17.81. $C_{17}H_{21}N_4O_2$. Calculated, %: C 65.17; H 6.76; N 17.88.

1-Hexyl-2-acetyl-3-keto-5-methyl-1,5-dihydropyridazino[4,3-b]quinoxaline (IVb) was obtained analogously to the foregoing from (Va) (2 g: 0.0063 mole) and acetic anhydride (20 ml). Yield was 60.5%, mp 104-107°C (from 40% aqueous alcohol). IR spectrum, ν, cm^{-1}: 1640, 1695 C=O). Found, %: C 67.30; H 7.34; N 16.60. $C_{19}H_{24}N_4O$. Calculated: C 67.20; H 7.07; N 16.50.

2-Acetyl-3-keto-5-methyl-10-butyl-5,10-dihydropyridazino[4,3-b]quinoxaline (VIa). A mixture of (Va) (1 g) and acetic anhydride (15 ml) was boiled for 3 h. The brown solid which separated on cooling was filtered off and washed with dry ether. Yield was 0.7 g (64.5%). mp 176-178°C. IR spectrum, ν, cm^{-1}: 1650, 1705 (C=O). Found, %: C 65.43; H 6.40; N 17.85. $C_{17}H_{20}N_4O_2$. Calculated, %: C 65.40; H 6.44; N 18.00.

3-Keto-5-methyl-10-butyl-5,10-dihydropyridazino[4,3-b]quinoxaline (VIIa). Method A. A mixture of (Va) (1.5 g: 0.0052 mole) and acetic anhydride (20 ml) was boiled for 3 h and the reaction mixture was poured into water (200 ml). The orange solid which separated was filtered off and washed with water. Yield was 0.8 g (55%) mp 261-263° (from acetic acid). IR spectrum, ν, cm^{-1}: 1640 (C=O), 3140, 3260 (NH). Found, %: C 66.91; H 6.75; N 21.79. $C_{15}H_{18}N_4O$. Calculated, %: C 66.80; H 6.65; N 20.80.

Method B. Phosphorus oxychloride (5.35 g: 0.035 mole) was added to dimethylformamide (DMF) (40 ml) with stirring and cooling below 5°C. The mixture was then cooled to 0°C and a solution of (Va) (2 g: 0.0069 mole) in DMF (30 ml) was added gradually. The mixture was left to stand at room temperature for 3 days. A solid gradually separated from the solution. The reaction mixture with the solid was poured onto ice. Orange crystals were filtered off. Yield was 79.5% mp 262-264°C (from 80% aqueous alcohol). IR spectrum, ν, cm^{-1}: 1640 (C=O), 3140, 3260 (NH). Found, %: C 66.02, H 6.51, N 20.09. $C_{15}H_{18}N_4O$. Calculated, %: C 66.54, H 6.71, N 20.73.

3-Keto-5-methyl-10-hexyl-5,10-dihydropyridazino [4,3-b]quinoxaline (VIIb). Compound (VIIb) was obtained similarly to the above by method A. Yield was 52.1% mp 264-267°C. IR spectrum, ν, cm^{-1}: 1640 (C=O), 3300 (NH). Found, %: C 68.56, H 7.58, N 18.46. $C_{17}H_{22}N_4O$. Calculated. %: C 68.50, H 7.40, N 18.80.

4-Formyl-3-keto-5-methyl-5,10-dihydropyridazino[4,3-b]quinoxaline (VIIa). Compound (VIIa) was obtained similarly to the above by method B from (Ia) (3 g). Yield was 80.2% mp 312-315°C (from acetic acid). IR spectrum, ν, cm^{-1}: 1630, 1650 (C=O), 3150 (NH). PMR spectrum, δ, ppm in D-DMSO: 6.7-7.3 (Ph), 3.15 (NCH_3), 9.93 (CHO), 11.70 and 11.10 wide singlet (NH). Found, %: C 59.72, H 4.09, N 23.16. $C_{12}H_{10}N_4O_2$. Molecular weight (here and subsequently mass spectrometrically) 242. Calculated, %: C 59.49, H 4.16, N 23.13. Molecular weight 242.

4-Formyl-3-keto-5-benzyl-5,10-dihydropyridazino[4,3-b]quinoxaline (VIIIb). Compound (VIIIb) was obtained from (Ib) (2 g). Yield was 24%, mp 317-318°C (from acetic acid). IR spectrum, ν, cm^{-1}: 1640, 1660 (C O), 3150 (NH). PMR spectrum, δ, ppm in D-DMSO: 6.6-7.4 (Ph), 5.03 (NCH_2), 7.32 (CH_2Ph). Found, %: C 68.34, H 4.72, N 17.87. $C_{18}H_{14}N_4O_2$. Molecular weight 318. Calculated, %: C 67.90, H 4.74, N 17.55. Molecular weight 318.

4-Formyl-3-keto-5,8-dimethyl-5,10-dihydropyridazino[4,3-b]quinoxaline (VIIIc). Compound (VIIIc) was obtained from (Ic) (4 g). Yield was 71% mp 318-320°C (from DMF). IR spectrum, ν, cm^{-1}: 1640, 1650 (C O), 3150 (NH). Found, %: C 60.73, H 4.70, N 22.05. $C_{13}H_{12}N_4O_2$. Calculated, %: C 60.93, H 4.72, N 21.86.

Phenylhydrazone of 4-Formyl-3-keto-5-methyl-5,10-dihydropyridazino[4,3-b]quinoxaline (IXa). A mixture of (VIIIa) (0.5 g) in alcohol (100 ml), phenylhydrazine (1 g), and acetic acid (1 ml) was boiled for 40 min. A precipitate formed in the brown solution. Yield was 43.5% mp 303-306°C (from alcohol). IR spectrum, ν, cm^{-1}: 1635 (C O), 3110, 3215, 3390 (NH). Found, %: C 65.22; H 4.75; N 25.36. $C_{18}H_{16}N_6O$. Calculated, %: C 65.04; H 4.85; N 25.28.

LITERATURE CITED

1. G. S. Predvoditeleva, T. V. Kartseva, T. N. Zykova, et al., Khim.-Farm. Zh., No. 6, 20 (1975).
2. G. S. Predvoditeleva, T. V. Kartseva, O. N. Oleshko, et al, Khim.-Farm Zh., No. 10, 53 (1977).
3. M. Israel and N. Tirosh, J. Med. Chem., 16, 520 (1973).
4. T. G. Koksharova, V. N. Konyukhov, Z. V. Pushkareva, et al., Khim. Geterosikl. Soedin., 247 (1972).
5. F. Ioneda and V. Vitta, Chem. Pharm. Bull., 11, 271 (1963).
6. T. V. Gortinskaya, V. G. Nyrkova, N. V. Savitskaya, et al., Khim.-Farm. Zh., No. 5, 8 (1972).
7. N. V. Savitskaya, V. V. Gortinskaya, V. G. Nyrkova, et al., Khim.-Farm. Zh., No. 4, 30 (1977).

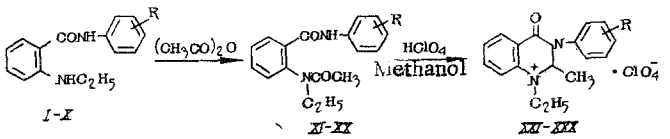
INVESTIGATIONS IN THE 4[3H]-QUINAZOLONE SERIES.

X. SYNTHESIS AND BIOLOGICAL ACTIVITY OF 1-ETHYL-2-METHYL-3-ARYL-4[3H]-QUINAZOLONIUM PERCHLORATES

Yu. V. Kozhevnikov, N. N. Smirnova, V. S. Zalesov, and I. I. Gradel'

UDC 615.213:547.856.1].012.1

It was established by us previously that 4[3H]-quinazolonium salts possess anticonvulsant activity [1]. As a development of these investigations the synthesis has been effected of N-ethylanthranilic acid arylamides and conversion of them into 1-ethyl-2-methyl-3-aryl-4[3H]-quinazolonium perchlorates



Arylamides (I-X: Table 1) were obtained by the method in [2]. Under the action of acetic anhydride they formed arylamides of N-ethyl-N-acetylanthranilic acid (XI-XX: Table 2) which cyclized on boiling in methanol in the presence of perchloric acid into 1-ethyl-2-methyl-3-aryl-4[3H]-quinazolonium perchlorates (XXI-XXX). Compounds (XXI-XXX) (Table 3) were colorless crystalline substances, soluble in organic solvents with difficulty, and were hydrolyzed by the action of 10% aqueous sodium hydroxide solution to compounds (XI-XX). On boiling in an aqueous alcoholic solution of sodium hydroxide they were hydrolyzed with the formation of the initial arylamides. The structures of compounds were confirmed by IR and PMR spectra. In the IR spectra of the arylamides bands characteristic of secondary amides were detected in the region of 1640, 1530, and 1320 cm^{-1} which were absent for the corresponding 4[3H]-quinazolonium compounds. In the IR spectra of the quinazolonium compounds bands were detected in the region of 1700-1715 cm^{-1} (Ar—C=O), 1620-1626, 1560-1567, 1470-1485 cm^{-1} (quinazolonium ring), and an intense band in the region of 1100-1122 cm^{-} was explained by

Perm Institute of Pharmacy. Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 15, No. 6, pp. 55-59, June, 1981. Original article submitted November 6, 1980.