RESEARCH INTO ANALOGS OF PYRAN AND RELATED COMPOUNDS

XXXI. The Reduction of 2,2-Dimethyl-4-chromanone Oximes*

N. V. Dudykina, L. M. Meshcheryakova, and V. A. Zagorevskii

Khimiya Geterotsiklicheskikh Soedinenii, Vol. 5, No. 3, pp. 434–439, 1969

UDC 547.814.1:542.942.6:541.67

The reduction of the oximes of 2,2-dimethyl-4-chromanone (I), 2,2,6-trimethyl-4-chromanone (II), and 2,2,5,7,8-pentamethyl-6-hydroxy-4-chromanone (III) with lithium aluminum hydride has been investigated. The first of these affords the normal reduction product 2,2-dimethyl-4-amino chroman (VI), which was also obtained by catalytic hydrogenation of the oxime. The second oxime is converted into a mixture containing the 4-aminochroman (VII) and the product of reductive ring expansion, 2,2,7-trimethyl-2,3,4,5-tetrahydro-1,5-benzoxazepine (VIII). From the oxime of III was obtained 2,2,6,8,9-pentamethyl-7-hydroxy-2,3,4,5-tetrahydro-1,5-benzoxazepine (IX), the structure of which was confirmed by determination of the basicity constants, the NMR spectra, and the preparation of the N-benzoyl derivatives (XI).

4-Aminochromanones and 2,3,4,5-tetrahydro-1,5-benzoxazepines may be obtained by the lithium aluminum hydride reduction of chromanone oximes [1, 2].

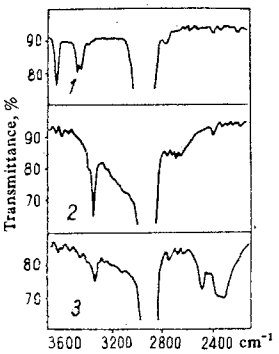


Fig. 1. IR spectra of 2,2,6,8,9-pentamethyl-7-hydroxy-2,3,4,5-tetrahydro-1,5-benzoxazepine (IX): 1) solution in CCl_4; 2) in oil; 3) deuterated compound, in oil.

4-Aminochromans and the corresponding tetrahydrobenzoxazepines bearing two alkyl groups in the 2-position are unknown, and since these could prove of interest for pharmacological evaluation, we have examined the lithium aluminum hydride reduction of the oximes of 2,2-dimethyl-4-chromanone (I), 2,2,6-trimethyl-4-chromanone (II), and 2,2,5,7,8-pentamethyl-6-hydroxy-4-chromanone (III). The latter ketone has been obtained previously [3, 4] in 3–4% yields by the condensation of trimethylhydroquinone with β,β-dimethylacryloyl chloride in nitrobenzene in presence of aluminum chloride or in the presence of anhydrous hydrogen fluoride, followed by a rather complicated purification involving adsorption chromatography. The low yields are doubtless attributable to polymerization and resinification, and possibly alkylation (but not acylation) of the hydroquinone by the unsaturated acid. In addition, in carrying out this reaction it is important to choose conditions favoring the ring closure of the intermediate substituted acryloylhydroquinone. Satisfactory results (40% yield) were obtained when we treated trimethylhydroquinone bis-β,β-dimethylacrylate (IV, readily obtained in good yield by reaction of trimethylhydroquinone with β,β-dimethylacryloyl chloride) with aluminum chloride in carbon disulfide. 2,2,5,7,8-Pentamethyl-6-hydroxy-4-chromanone was prepared in the usual way. The formation of this compound apparently proceeds by the Fries rearrangement of the ester IV, followed by cyclization of the intermediate acryloylhydroquinone with simultaneous fission of the second acyl group. 2,2-Dimethyl-4-chromanone has been obtained previously by reaction of phenyl dimethylacrylate with aluminum chloride in absence of a solvent [5]. We have, however, been unable to attain yields of more than 5% instead of the stated 45% (on crude product). A sufficiently high yield of about 20% has been achieved by carrying out the reaction in carbon disulfide. 2,2,6-Trimethyl-4-chromanone has been synthesized by Auwers [6] (without indication of yield) by the reaction of p-methoxytoluene with dimethylacryloyl chloride and aluminum chloride; other reaction products were formed

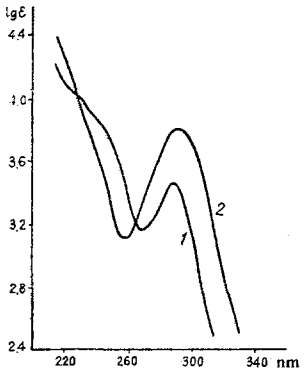
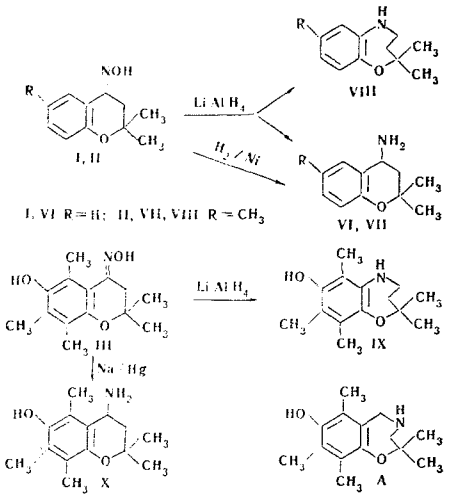


Fig. 2. UV spectra: 1) 2,2,6,8,9-pentamethyl-7-hydroxy-2,3,4,5-tetrahydro-1,5-benzoxazepine (IX); 2) 2,2,5,7,8-pentamethyl-4-amino-6-hydroxychroman (X) (ethanol, $c = 1 \cdot 10^{-4} - 1 \cdot 10^{-3}$).

that were separated only with difficulty. We have obtained this ketone in 32% yield from p-cresyl dimethacrylate (V) by treatment with aluminum chloride.

*For part XXX, see [14].

Oximes I and III have not been described in the literature. Reduction of I with lithium aluminohydride in ether gave the normal reaction product, 2,2-dimethyl-4-aminochroman (VI), in 57% yield. We were unable to isolate the isomeric compound. Structure VI was confirmed by conversion to the N-benzoyl derivative, the IR spectrum of which showed the NH stretching band.



Hydrogenation of I over skeletal nickel under usual conditions proceeded extremely sluggishly to give the same amine VI. Reduction of the oxime II by lithium aluminum hydride afforded 42% of 2,2,6-trimethyl-4-aminochroman (VII) and 17% of the ring-expansion product 2,2,7-trimethyl-2,3,4,5-tetrahydro-1,5-benzoxazepine (VIII). Reduction of the oxime III by lithium aluminum hydride in ether proceeded very slowly as a result of the precipitation of the phenoxide. A compound with the composition $C_{14}H_{21}NO_2$ was isolated from the reaction mixture, mp 150–151° C. The IR spectrum (in CCl_4) of this compound (Fig. 1, curve 1) shows a band at 3640 cm^{-1} in the 3100–3700-cm^{-1} region, due to the phenolic hydroxyl, and a somewhat less intense, split band with peaks at 3420 and 3460 cm^{-1}. These results did not permit the definite assignment to the compound of the structure IX or X, and the UV spectrum was therefore obtained (Fig. 2, curve 1). The position and intensity of the long-wave maximum (290 nm, log ε 3.46) agreed with those of α-tocopherol [7]. This did not exclude the possibility of the structure X.

We attempted to synthesize compound X by the catalytic reduction of the oxime III over palladium and skeletal nickel, by treatment with tin and hydrochloric acid, zinc and acetic acid, sodium and methanol in liquid ammonia, and sodium in isoamyl alcohol, but without success. Only by reduction with 1.25% sodium amalgam in acetic acid was the oxime converted into the aminochroman X in 25% yield. By its mp (126–127° C), by some other properties, and by its UV spectrum (Fig. 2, curve 2), the aminochroman X differed from compound IX. Monobenzoylation of IX gave the corresponding anilide (XI). The IR spectrum (in chloroform) of XI showed in the 3100–3700-cm^{-1} region only one band, at 3620 cm^{-1}, attributable to the phenolic hydroxyl. An extremely intense band appeared in the 1500–1800-cm^{-1} region at 1632 cm^{-1} (primary amide), a low intensity band at 1595 cm^{-1} (benzene ring), and no band due to a secondary amide. This anilide is consequently a derivative of a secondary amine.

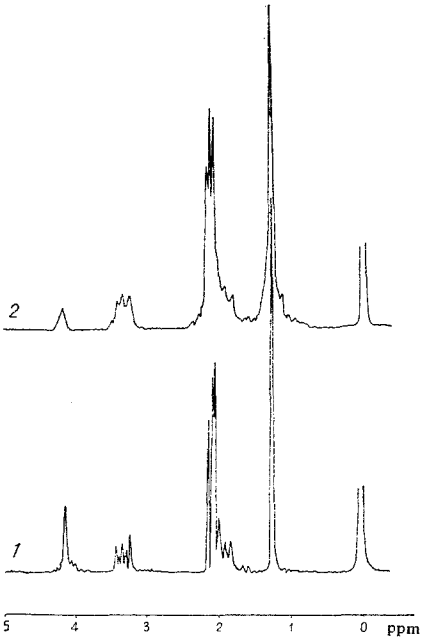


Fig. 3. NMR spectrum of 2,2,6,8,9-pentamethyl-7-hydroxy-2,3,4,5-tetrahydro-1,5-benzoxazepine (IX) in deuterochloroform: 1) nondeuterated compound; 2) deuterated compound.

However, a final choice in favor of structure IX cannot be made for the following reasons. There has recently appeared in the literature some information on the alkyl-migration-type Beckmann rearrangement of oximes of ketones of the 1-tetralone and 4-chromanone types [8–10]. Since the formation of ring-enlarged products on reduction of the appropriate ketoximes is thought to result from the initial occurrence of a Beckmann rearrangement [1, 11, 12], our hydrobenzoxazepines could possess structure A, not IX. The structure IX was confirmed by determination of the basicity constant and the NMR spectrum. The pK_a value (determined by I. V. Persianova, to whom we express our thanks), measured in 50% ethanol, was 4.97, a value characteristic for amines of the aniline series (see, for example, [13]). The NMR spectrum (obtained by E. I. Fedin, to whom the authors express sincere thanks; spectra were recorded in chloroform on a Hitachi H-60 instrument with a working frequency of 60 MHz, δ-scale, internal standard hexamethyldisiloxane) has the following signals (Fig. 3, curve 1): 1.25 ppm, singlet due to the protons of the two equivalent gem-methyl groups at C_2; 2.05, 2.08, and 2.13 ppm, signals which were not fully resolved, due to the protons of the three methyl groups attached to the benzene ring; 3.30 ppm, triplet (J = 6 Hz), due to the protons of the N—CH_2 methylene group, coupling with the neighboring CH_2 group (insufficient resolution of the latter triplet resulted in partial overlapping with the protons of the aromatic CH_3 groups in

the 1.7–2.0-ppm region); 4.15 ppm, singlet of area 2 proton units, caused apparently by exchange of the protons of the OH and NH groups. No signals were observed at lower fields, down to 12 ppm. The attribution of the signals at 4.15 ppm to labile protons was confirmed by the NMR spectrum of partially deuterated IX. Deuteration was carried out by boiling for several hours with D_2O in dioxane solution. Comparison of the IR spectra in oil of the deuterated and nondeuterated compounds (Fig. 1, curves 2 and 3) showed that a substantial degree of deuteration had occurred. In agreement with this, the NMR spectrum of the deuterated compound IX (Fig. 3, curve 2) showed that the area of the signal at 4 ppm had been reduced to 0.6 proton unit.

In order to avoid the separation of the insoluble phenate during the reduction of the oxime III by lithium aluminum hydride, we used its O,O'-diacetyl derivative (XII). The reaction in this case proceeded in solution appreciably more quickly, to give IX in better yield (56%).

EXPERIMENTAL

Trimethylhydroquinone bis-(β,β-dimethylacrylate) (IV). To 6.08 g (0.04 mole) of trimethylhydroquinone in 20 ml of benzene was added dropwise 9.44 g (0.08 mole) of β,β-dimethylacryloyl chloride; the mixture was heated for 1 hr on the water bath, the hydrogen chloride evolved being evacuated, and cooled. About 200 ml of water was added; the mixture was extracted with ether, the extract washed with 5% NaOH, evaporated, and dried by addition and distillation of benzene (finally in vacuo). There was obtained 11.8 g (93%) of IV, mp 105–106° C (from benzene). Found, %: C 72.47, 72.44; H 7.63, 7.63. Calculated for $C_{19}H_{24}O_4$, %: C 72.12; H 7.64.

2,2,5,7,8-Pentamethyl-6-hydroxy-4-chromanone. To 38.2 g (0.127 mole) of finely ground diester IV and 19.1 g (0.143 mole) of $AlCl_3$ was added 70 ml of CS_2, and the mixture was heated at 70–100° C (bath temp) for 2 hr, the CS_2 distilled off (finally in vacuo), the residue heated with stirring to 140–150° C (bath temp) for 10–15 min, and the cooled mixture decomposed with about 170 ml of 18% HCl in the presence of ether. The ether layer was separated, washed with water, 5% $NaHCO_3$, dried over Na_2SO_4 and evaporated. The brown oil (26.6 g) was triturated with acetone, and the resulting crystals washed with acetone to give 9.6 g of material, mp 159–160° C. The mother liquors were evaporated, the residue dissolved in ether, and the solution extracted twice with 5% NaOH. The alkaline extract was filtered during 48 hr and acidified with HCl and then extracted with ether. The ethereal extract was washed with water, evaporated, and the residue triturated with acetone to give a further 2 g of the ketone. The over-all yield was 11.6 g (41.4%), mp 160–161° C (from acetone). Lit. mp 162° C [4], 156–158° C [3].

2,2,5,7,8-Pentamethyl-6-hydroxy-4-chromanone oxime (III). To a hot solution of 10.11 g (0.043 mole) of the ketone in 60 ml of methanol was added a solution of 3 g (0.13 mole) of hydroxylamine hydrochloride in 60 ml of methanol, followed by the slow addition of a solution of 4.3 g (0.107 mole) of NaOH in 65 ml of methanol. The mixture was boiled for 15 hr, evaporated in vacuo, water added to the residue, and the whole extracted with ether. The ether extract was washed with water, evaporated to dryness, the residue dried by addition and distillation of benzene, and recrystallized from benzene to give 3.43 g (88%) of the oxime III, mp 139.5–140° C. Found, %: C 67.46, 67.67; H 7.61, 7.46; N 5.68, 5.55. Calculated for $C_{14}H_{19}NO_3$, %: C 67.44; H 7.68; N 5.61.

2,2,5,7,8-Pentamethyl-4-amino-6-hydroxychroman (X). To 0.5 g (2 mM) of oxime II in 5 ml of ethanol was added gradually liquid 1.25% sodium amalgam (from 32 g Hg and 0.4 g Na), with simultaneous addition of 5 ml of acetic acid. The mixture was boiled for 4 hr, the solution decanted from the mercury, acidified with hydrochloric acid and evaporated to dryness. The residue was dissolved in water, the solution washed with ether (0.35 g of starting oxime was extracted), basified with sodium carbonate, and extracted with ether. Removal of the ether left 0.12 g (25%) of the amine X, mp 126–127° C (from ether). R_f 0.20 (Al_2O_3, grade VI activity, benzene). UV spectrum (ethanol): λ_{max} 294 nm (log ε 3.81). Found, %: C 71.13, 71.21; H 8.92, 9.18. Found, %: Cl 13.38, 13.38; N 4.94. Calculated for $C_{14}H_{21}NO_2 \cdot HCl$, %: Cl 13.09; N 5.15.

Diacetate (XII). To a warm solution of 1.25 g (5 mM) of the oxime III in 10 ml of dry pyridine was gradually added 1.6 g (0.02 mole) of acetyl chloride, and the mixture warmed gently for 2–3 min, then stirred for 15 min without heating and poured into about 350 ml of cold water. The precipitate was isolated to give 1.45 g (86%) of the diacetate XII, mp 137–138° C (from methanol). Found, %: C 65.06, 65.29; H 7.12, 7.00. Calculated for $C_{18}H_{23}NO_5$, %: C 64.86; H 6.95.

Reduction of diacetate XII. To a solution of 1.02 g (27 mM) of lithium aluminum hydride in 30 ml of ether (prepared in all cases from lithium hydride and $AlBr_3$) was gradually added 1 g (3 mM) of the diacetate XII in 35 ml of ether, the mixture boiled for 3.5 hr, decomposed with moist ether, and 30 ml of 18% HCl added. The precipitated hydrochloride was isolated and crystallized from methanol with the addition of ether, giving 0.45 g (56%) of the hydrochloride of amine IX, mp 212–213° C. Found, %: Cl 12.86; N 5.22. Calculated for $C_{14}H_{21}NO_2 \cdot HCl$, %: Cl 13.09; N 5.15. In the methanol-ether mother liquors from the crystallization of the hydrochloride, chromatography revealed the presence of another compound, probably the normal reduction product, which was not isolated in the pure state. Treatment of 0.5 g of the hydrochloride with 10% NaOH gave 0.4 g of the base IX, mp 150.5–151.5° C (from benzene), R_f 0.35 (Al_2O_3, grade VI activity, benzene). UV spectrum (in ethanol): λ_{max} 290 nm (log ε 3.46), inflection 240 nm (log ε 3.90). pK_a 4.97 ± 0.07 (measured in 50% v/v ethanol at 20° C, by potentiometric titration using a glass electrode on an LPU-01 pH meter). Found, %: C 71.62, 71.69; H 9.12, 9.00. Calculated for $C_{14}H_{21}NO_2$, %: C 71.45; H 8.99.

N-Benzoyl derivative XI. (Obtained by treatment of base IX with benzoyl chloride in triethylamine), mp 207–208° C (from acetone). Found, %: C 74.34, 74.50; H 7.39, 7.57. Calculated for $C_{21}N_{25}NO_3$, %: C 74.37; H 7.40.

2,2,-Dimethyl-4-chromanone. To finely ground $AlCl_3$ (34.7 g, 0.26 mole) in 25 ml of CS_2 was added slowly 36.8 g (0.80 mole) of phenyl dimethylacrylate, and the mixture was boiled for 2 hr. The CS_2 was distilled off (finally in vacuo), the temperature of the bath gradually raised during 10–15 min to 145–150° C, kept at this temperature for 10–15 min, and heating discontinued and the reaction mixture cooled to about 20° C. The resulting melt was treated simultaneously with ether and 18% HCl, the ether layer separated and extracted with 7% NaOH (5 × 20 ml), dried over Na_2SO_4, evaporated, and the residue washed with acetone and light petroleum to give 5.17 g of 2,2-dimethyl-4-chromanone. A further 1.3 g was obtained from the acetone solution. On keeping, more of this compound separated from the alkaline solutions, and it was isolated by extraction with ether to give a further 1 g of the ketone. Over-all yield 7.48 g (20.3%), mp 87–88° C [5].

2,2-Dimethyl-4-chromanone oxime (I). To a solution of 2.82 g (0.01 mole) of 2,2-dimethylchromanone in 35 ml of ethanol was added a solution of 3.3 g (0.047 mole) of hydroxylamine hydrochloride in 15 ml of water, followed by a solution of 1.6 g (0.04 mole) of NaOH in 10 ml of water. The mixture was boiled for 4 hr and evaporated in vacuo; water and ether were added to the residue, and the ether layer washed with water and evaporated. The residue (2.95 g) crystallized from methanol to give 1.9 g (88%) of the oxime I, mp 124–125° C. Found, %: C 69.26, 68.98; H 6.90, 6.91; N 7.60, 7.65. Calculated for $C_{11}H_{13}NO_2$, %: C 69.09; H 6.85; N 7.32.

2,2-Dimethyl-4-aminochroman (VI). To a solution of 1.05 g of lithium aluminum hydride in 30 ml of ether was added 1.8 g (9 mM) of I in 20 ml of ether; the mixture was boiled for 12 hr and then decomposed with moist ether and 20 ml of 10% NaOH. The ether layer was

extracted with 10% HCl (the ether layer contained 0.3 g of the starting oxime), the acid solution evaporated to dryness, the residual hydrochloride converted to the base by treatment with sodium carbonate, and the base extracted with ether. The hydrochloride was precipitated from the dry ether solution and was crystallized from methanol with the addition of ether, giving 1.15 g (56.7%) of the hydrochloride of amine **VI**, mp >330° C, which on chromatography on grade VI alumina gave a single spot. Found, %: Cl 16.38, 16.35; N 6.58. Calculated for $C_{11}H_{15}NO \cdot HCl$, %: Cl 16.6; N 6.55; **N-Benzoyl derivative,** mp 149–150° C (from ether). Found, %: C 76.76; H 6.80. Calculated for $C_{18}H_{19}NO_2$, %: C 76.85; H 6.80.

Hydrogenation of the oxime **I** over skeletal nickel under the usual conditions for 4 hr gave, in addition to unchanged oxime (84%), 12% of the hydrochloride of the amine **VI**, mp >330° C, identical by chromatography with a sample prepared as described above.

p-Cresyl β,β-dimethylacrylate (V). To 10.8 g (0.1 mole) of p-cresol was gradually added 11.8 g (0.1 mole) of β,β-dimethylacryloyl chloride; the mixture was heated at about 100° C for 1.5 hr, cooled, water added and extracted with ether. The ether extract was washed with 5% NaOH, dried, and distilled, giving 16.7 g (87%) of the ester V, bp 100–101° C (1 mm), n_D^{20} 1.5240. Found, %: C 75.58, 75.45; H 7.45, 7.40. Calculatedd for $C_{12}H_{14}O_2$, %: C 75.78; H 7.40.

2,2,6-Trimethyl-4-chromanone. This was prepared in the same way as 2,2-dimethylchromanone, using 33.2 g of $AlCl_3$, 40 ml of CS_2, and 38 g of the ester V. The ether extract was washed with 25% NaOH and distilled to give 12.3 g (32%) of the ketone, bp 117–120° C (3 mm). Lit. bp [6], 161–162° C (28–29 mm). The oxime II was obtained similarly to **III** in 30% yield, mp 129.5–131° C.

Reduction of 2,2,6-trimethyl-4-chromanone oxime (II). To 1.14 g (0.03 mole) of lithium aluminum hydride in 35 ml of ether was added 2.05 g (0.01 mole) of the oxime II in 20 ml of ether. The mixture was boiled for 12 hr and decomposed with moist ether and 10% HCl; the ether layer was separated (it contained 17% of starting oxime) and from the acid solution were separated a primary amine fraction (**VII**) and a secondary amine fraction (VIII), utilizing their different basicities by the previously described method [2]. The amine **VII** was converted into its hydrochloride (0.95 g, 42%), mp 264–265° C (from methanol and ether), R_f 0.32 (Al_2O_3, grade VI activity, benzene). Found, %: C 63.42, 63.49; H 8.10, 8.11; Cl 15.63, 15.59. Calculated for $C_{12}H_{17}ON \cdot HCl$, %: C 63.29; H 7.96; Cl 15.56.

Amine VIII was also converted into its hydrochloride in a yield of 0.4 g (17.6%), mp 194° C (decomp), R_f 0.65. The UV spectrum (in ethanol): λ_{max} 245 mm (log ε 3.57), 289 nm (log ε 3.19). Found, %: C 63.01, 62.87; H 7.84, 7.82; Cl 15.83. Calculated for $C_{12}H_{17}ON \cdot HCl$, %: C 63.23; H 7.96; Cl 15.56.

REFERENCES

1. V. A. Zagorevskii and N. V. Dubykina, ZhOKh, **34**, 2282, 1964.

2. N. V. Dubykina and V. A. Zagorevskii, The Synthesis of Natural Compounds and of Their Analogs and Fragments [in Russian], Nauka, 134, 1965.

3. W. John, Ph. Gunter, and M. Schmiel, Ber., **71**, 2637, 1938.

4. H. Offe and W. Barkow, Ber., **80**, 464, 1947.

5. W. Backer et al., J. Chem. Soc., 2010, 1956.

6. K. Auwers, Ann., **421**, 1, 1920.

7. O. Emerson et al., J. Biol. Chem., **122**, 99, 1937.

8. D. Huckle, I. Lockhart, and M. Wright, J. Chem. Soc., 1137, 1965.

9. D. Evans and I. Lockhart, J. Chem. Soc., 4806, 1965.

10. D. Lansburg and N. Mancuso, Tetrah. Let., 2445, 1965.

11. K. Lyle and H. Troscianiec, J. Org. Chem., **20**, 1757, 1955.

12. M. Harfenist and E. Magien, J. Am. Chem. Soc., **80**, 6080, 1958.

13. N. I. Kudryashova and N. V. Khromov-Borisov, ZhOrKh, **2**, 578, 1966.

14. E. K. Orlova, I. D. Tsvetkova, V. S. Troitskaya, V. G. Vinokurov, and V. A. Zagorevskii, KhGS [Chemistry of Heterocyclic Compounds], 429, 1969.

19 December 1966

Institute of Pharmacology and Chemotherapy AMS USSR, Moscow