Chemistry of Heterocyclic Compounds, Vol.35, No. 3, 1999

PYRROLOPYRIMIDINES.

3.* 5-AMINO-1,3-DIMETHYLPYRROLO-[3,2-*d*]PYRIMIDINE-2,4-DIONE

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Reaction of 5-amino-1,3-dimethylpyrrolo[3,2-d]pyrimidine-2,4-(1H,3H)-diones with β-diketones produces enaminoketones. Some of these are converted by Lewis acids into pyrrolopyridazines.

N-Aminoindoles react with β-dicarbonyl compounds to form enaminoketones that can then be converted to pyridazino[2,3-*a*]indoles [2-4]. It seemed interesting to investigate similar reactions with 5-amino-1,3-dimethylpyrrolo[3,2-*d*]pyrimidine-2,4-(1H,3H)-diones (Ia,b) that were recently synthesized by us [1]. The β-dicarbonyl compounds used in the present work were acetylacetone (II), dibenzoylmethane (III), 5,5-dimethylcyclohexane-1,3-dione (IV) and the triketones 2-acetyl-5,5-dimethylcyclohexane-1,3-dione (V) and 2-acetylindane-1,3-dione (VI) and the tetraketone oxalyldiacetophenone (VII). Heating Ia or Ib with an excess of II or IV-VI without solvent at 140-200°C produces the corresponding enaminoketones VIIIa,b, IXa,b, X and XI.

Condensation with III under these conditions does not occur. With VII, a complicated mixture of compounds that could not be identified is formed.

According to PMR spectra, VIIIa,b and IX exist in the *Z*-form stabilized by an intramolecular hydrogen bond (IHB) between the NH proton and the ketone carbonyl. This is consistent with the position of the signal of the NH proton at 12.2-12.3 ppm, as noted before in the literature [4]. The NH signal in X is observed at 9.3 ppm. This would apparently suggest the formation of a weaker IHB in this instance. In IXa,b, where an IHB is impossible,*[2] the signal of the NH proton appears at 7.2-7.3 ppm, which is typical of unchelated NH protons.

The fact that pyridazines do not form along with the enaminoketones, like in the reaction of 1-aminoindole with acetylacetone [4], is probably due to the lower nucleophilicity of the pyrrole ring of amines Ia,b compared with indole [7]. However, enamine VIIIa, in analogy with the corresponding indole derivative [4], converted into the pyridazine XII on treatment with BF_3 etherate in acetonitrile.

Pyridazine XII is also produced on heating Ia with acetylacetone and BF_3 etherate or anhydrous $ZnCl_2$ without isolation of the intermediate enaminoketone. The amine Ia and dibenzoylmethane form XIII under analogous conditions. Resinous substances, among which only acetophenone could be identified, resulted from an attempt to carry out a similar reaction of Ia and oxalyldiacetophenone. Condensing the 7-bromo-substituted amine

* For No. 2, see [1].

*[2] Theoretically the NH proton could form an IHB with the amide carbonyl of the uracil core. However, judging from X-ray structure analyses of 1-formylaminoindazole [5] and 1-(N-nitrosomethylamino)benzimidazole [6], which are isoelectronic with VIII-XI, the whole N-amino substituent is twisted relative to the heteroaromatic system by almost 90°. Thus, the amine nitrogen atom is sp^2-hybridized. Such a geometry, which precludes an IHB of the NH and the carbonyl $C_{(4)}$=O, most probably also occurs in VIII-XI.

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Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 3, pp. 375-380, March, 1999. Original article submitted February 12, 1998.

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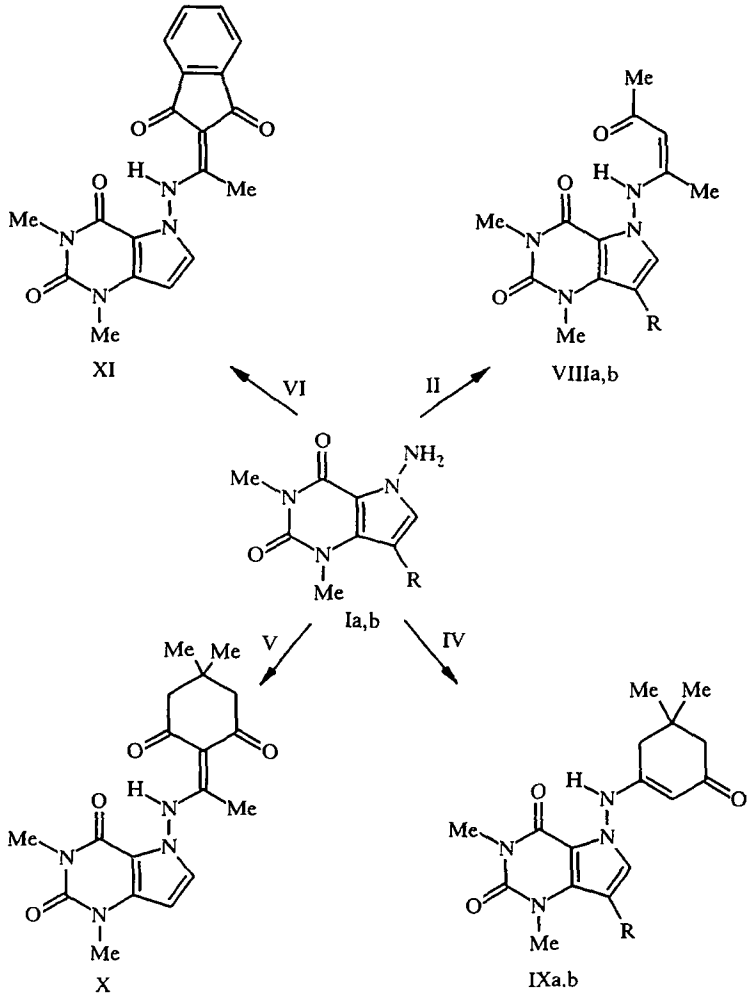
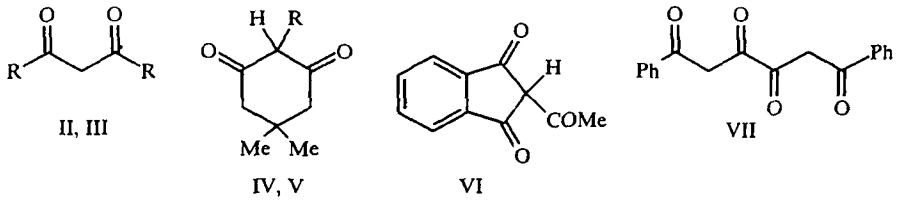
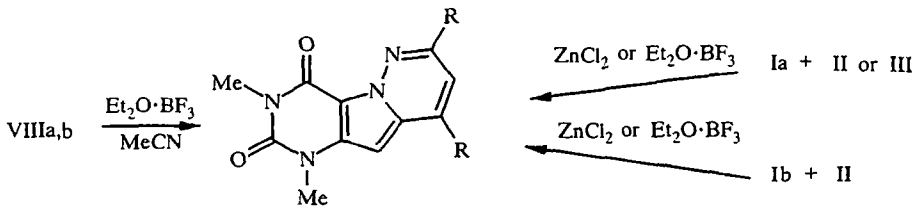


VIIIa, IXa R = H; VIIIb, IXb R = Br



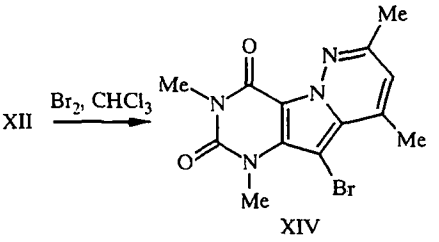
II R = Me, III R = Ph, IV R = H, V R = MeCO

Ib with acetylacetone in the presence of either BF_3 etherate or $ZnCl_2$ produced not the expected XIV but the pyridazine XII, in which bromine was absent. Pyridazine XIV was prepared in 87% yield by reacting XII with Br_2 in $CHCl_3$ at room temperature. Bromine could not be introduced into the pyrrole ring of XIII under the same conditions. This is probably due to steric factors.



XII R = Me, XIII R = Ph

In order to determine in which reaction step bromine atom on the pyrrole ring is replaced by hydrogen atom, model compounds IXb and N-(7-bromo-1,3-dimethylpyrrolo[3,2-*d*]pyrimidin-5-yl)acetamide (XV), which cannot form pyridazine derivatives because of their structure, were heated with acetylacetone in the presence of BF_3 etherate. As it turned out, XV under these conditions is unreactive whereas IXb converts to XII, apparently as a result of the reimination with acetylacetone and subsequent cyclization of the intermediate VIIIb.



Obviously the protodebromination occurs either during the cyclization of the enamine into pyridazine or after its conversion. As it turned out, bromine atom is replaced by hydrogen atom in XIV during heating with acetylacetone or phenol even without Lewis acids. It can be proposed that XIV is thermodynamically very unstable because of steric hindrance created for the bromine atom by the two methyl groups in the 1- and 9-positions. Therefore, the protodebromination occurs readily even in the presence of weak acids.

Enaminoketones X and XI could not be cyclized into the corresponding pyridazines (for example, by heating X with $ZnCl_2$ in dioxane) although the cyclohexenone carbonyl can undergo such a cyclization reaction according to the literature [8]. However, heating X in acetylacetone with BF_3 etherate, like for IXb, forms XII. On the other hand, XI under analogous conditions does not react. This fact confirms our hypothesis that the exocyclic carbonyl of the acetyl derivatives of dimedone and indanedione condense with the amino group. Otherwise the cyclization by Lewis acids should proceed with ease. The β-carbonyl group in X and XI is rigidly fixed in the ring and therefore probably only with difficulty can twist into a position suitable for attack at the α-position of the pyrrole ring to form the pyridazine ring.

EXPERIMENTAL

IR spectra were obtained on an IKS-40 spectrometer from solutions in $CHCl_3$. PMR spectra were measured in $CDCl_3$ on a Varian UNITI 300 (300 MHz) spectrometer. Chemical shifts are given as δ *vs.* TMS. The course of the reactions and the purity of the products were monitored using Silufol UV-254 plates and II-grade activated Al_2O_3. The eluent was $CHCl_3$. Iodine vapor was used for visualization.

1,3-Dimethyl-5-[(*Z*)-1-methyl-3-oxo-1-butenylamino]pyrrolo[3,2-*d*]pyrimidine-2,4(1H,3H)-dione (VIIIa). Solution of Ia (0.2 g, 1 mmol) in acetylacetone (5 ml) was boiled for 2 h. The excess of acetylacetone was distilled off. The solid was recrystallized from alcohol (colorless prisms). Yield 0.25 g (89%); mp 173-175°C. IR spectrum: 3115 (NH), 1693, 1650, 1629 cm^{-1} (CO). PMR spectrum: 12.23 (1H, br. s, NH), 7.02 (1H, d, J = 3.22 Hz, 6-H), 5.96 (1H, d, J = 3.22 Hz, 7-H), 5.34 (1H, s, CH), 3.47 (3H, s, 1-CH_3), 3.37 (3H, s, 3-CH_3), 2.16 (3H, s, CH_3), 1.76 ppm (3H, s, CH_3). Found, %: C 56.25; H 5.33; N 20.56. $C_{13}H_{16}N_4O_3$. Calculated, %: C 56.51; H 5.84; N 20.28.

7-Bromo-1,3-dimethyl-5-[(*Z*)-1-methyl-3-oxo-1-butenylamino]pyrrolo[3,2-*d*]pyrimidine-2,4(1H,3H)-dione (VIIIb) was prepared analogously to VIIIa from Ib (0.28 g, 1 mmol) with a yield of 0.22 g (61%). Colorless needles from alcohol; mp 179-180°C. IR spectrum: 3181 (NH), 1701, 1661, 1626 cm^{-1} (CO). PMR spectrum: 12.23 (1H, br. s, NH), 7.06 (1H, d, J = 3.22 Hz, 6-H), 5.35 (1H, s, CH), 3.80 (3H, s, 1-CH_3), 3.36 (3H, s, 3-CH_3), 2.17 (3H, s, CH_3), 1.77 ppm (3H, s, CH_3). Found, %: C 44.10; H 4.22; Br 22.46; N 15.53. $C_{13}H_{15}BrN_4O_3$. Calculated, %: C 43.96; H 4.26; Br 22.50; N 15.77.

5-(5,5-Dimethyl-3-oxo-1-cyclohexenylamino)-1,3-dimethylpyrrolo[3,2-*d*]pyrimidine-2,4(1H,3H)-dione (IXa). Mixture of Ia (0.2 g, 1 mmol) and dimedone IV (1 g, 7.1 mmol) was stirred at 170-190°C until evolution of water stopped (5-7 min). Alcohol (4 ml) was added to the cooled melt and heated with stirring until boiling. The colorless or slightly greenish crystals that formed on cooling were filtered off and washed with alcohol. Yield 0.23 g

(70%). Needles from alcohol; mp 267-268°C. IR spectrum: 3380, 3240 (NH), 1700, 1660, 1640 cm^{-1} (CO). PMR spectrum: 7.30 (1H, br. s, NH), 7.05 (1H, d, J = 3.07 Hz, 6-H), 5.95 (1H, d, 7-H), 4.60 (1H, s, CH), 3.47 (3H, s, 1-CH_3), 3.34 (3H, s, 3-CH_3), 2.38 (2H, s, CH_2), 2.23 (2H, s, CH_2), 1.13 ppm (6H, s, 2CH_3). Found, %: C 60.92; H 6.30; N 17.34. $C_{16}H_{20}N_4O_3$. Calculated, %: C 60.75; H 6.37; N 17.71.

7-Bromo-5-(5,5-dimethyl-3-oxo-1-cyclohexenylamino)-1,3-dimethylpyrrolo[3,2-*d*]pyrimidine-2,4(1H,3H)-dione (IXb). The synthesis is performed analogously to that for IXa from Ib (0.28 g, 1 mmol) and dimedone IV (1 g, 7.1 mmol). Acetonitrile (6 ml) is added to the melt and heated to boiling with stirring. The resulting suspension is cooled to 60-65°C. The crystals are filtered off and wahsed with acetonitrile (10 ml) and then alcohol (3 ml). Yield 0.22 g (54%). Colorless crystals from alcohol; mp 233-234°C. IR spectrum: 3200 (NH), 1700, 1660, 1630 cm^{-1} (CO). PMR spectrum: 7.40 (1H, br. s, NH), 7.10 (1H, s, 6-H), 4.61 (1H, s, CH), 3.79 (3H, s, 1-CH_3), 3.34 (3H, s, 3-CH_3), 2.38 (2H, s, CH_2), 2.22 (2H, s, CH_2), 1.13 ppm (6H, s, 2CH_3). Found, %: C 48.36; H 5.21; Br 19.86; N 14.32. $C_{16}H_{19}BrN_4O_3$. Calculated, %: C 48.62; H 4.85; Br 20.22; N 14.17.

5-[1-(4,4-Dimethyl-2,6-dioxocyclohexenylidene)ethylamino]-1,3-dimethylpyrrolo[3,2-*d*]pyrimidine-2,4(1H,3H)-dione (X). The synthesis is performed analogously to that for IXa from Ia (0.2 g, 1 mmol) and 2-acetyldimedone V (1.3 g, 7.1 mmol). Ethanol (5 ml) is added to the melt and stirred. Colorless crystals are filtered off and washed with alcohol (5 ml) and acetone. Yield 0.29 g (78%); mp 261-262°C (alcohol). IR spectrum: 3460 (NH), 1700, 1660, 1600, 1580 cm^{-1} (CO). PMR spectrum: 9.26 (1H, br. s, NH), 7.00 (1H, d, J = 3.21 Hz, 6-H), 6.06 (1H, d, 7-H), 3.48 (3H, s, 1-CH_3), 3.35 (3H, s, 3-CH_3), 2.54 (2H, s, CH_2), 2.42 (2H, s, CH_2), 2.36 (3H, s, CH_3), 1.08 ppm (6H, s, 2CH_3). Found, %: C 60.55; H 6.24; N 15.72. $C_{18}H_{22}N_4O_4$. Calculated, %: C 60.32; H 6.19; N 15.63.

5-[1-(1,3-Dioxo-2,3-dihydro-1H-2-indenylidene)ethylamino]-1,3-dimethylpyrrolo[3,2-*d*]pyrimidine-2,4(1H,3H)-dione (XI). The synthesis is performed analogously to that for IXa from Ia (0.2 g, 1 mmol) and 2-acetylindanedione VI (0.55 g, 2.9 mmol). Ethanol (5 ml) is added to the melt and stirred. Crystals are filtered and washed with alcohol (3 ml). Yield 0.28 g (74%). Yellow crystals with mp 289-290°C (alcohol). IR spectrum: 3490, 3150 (NH), 1710, 1665, 1598, 1590 cm^{-1} (CO). PMR spectrum: 12.34 (1H, br. s, NH), 7.81-7.64 (4H, m, H_{Ph}), 7.09 (1H, d, J = 3.20 Hz, 6-H), 6.09 (1H, d, 7-H), 3.55 (3H, s, 1-CH_3), 3.36 (3H, s, 3-CH_3), 2.43 ppm (3H, s, CH_3). Found, %: C 62.95; H 4.36; N 15.47. $C_{19}H_{16}N_4O_4$. Calculated, %: C 62.63; H 4.43; N 15.38.

1,3,7,9-Tetramethylpyrimido[4',5':4,5]pyrrolo[1,2-*b*]pyridazine-2,4(1H,3H)-dione (XII). A. Boiling solution of VIIIa (0.28 g, 1 mmol) in acetonitrile (14 ml) is treated with BF_3 etherate (0.1 g, 0.7 mmol) and boiled for 1 h. The reaction mixture is cooled. The precipitate is filtered off and washed with water (4 ml). Yield 0.15 g (57%). Crystallization from acetonitrile produced colorless or light yellow crystals of XII; mp 310°C. IR spectrum: 1700, 1670 cm^{-1} (CO). PMR spectrum: 6.70 (1H, q, J = 1.1 Hz, 8-H), 6.08 (1H, s, 10-H), 3.56 (3H, s, 1-CH_3), 3.49 (3H, s, 3-CH_3), 2.60 (3H, s, 7-CH_3), 2.49 ppm (3H, d, 9-CH_3). Found, %: C 60.40; H. 5.35; N. 21.56. $C_{13}H_{14}N_4O_2$. Calculated, %: C 60.46; H 5.46; N 21.69.

B. Compound XII was synthesized analogously to method A from VIIIb (0.36 g, 1 mmol). The acetonitrile is evaporated to dryness. The solid is ground with ammonia (1.4 ml, 25%) and water (9 ml). The product is filtered off, washed with water, and recrystallized from acetonitrile with activated charcoal. Yield 0.11 g (44%); mp 306-308°C.

C. Boiling solution of Ia (1 g, 5.15 mmol) in acetylacetone (5 ml) is treated dropwise with BF_3 etherate (1.46 g, 10.3 mmol). The reaction mixture almost immediately hardens. Water (1.2 ml) is added and boiled for 3 min more. The hot mixture is suspended in acetonitrile (20 ml) and cooled. The precipitate is filtered off and washed with acetonitrile. Yield 1.21 g (91%). Crystallization from acetonitrile produces crystals of II with mp 310°C.

D. Compound XII is prepared similarly from Ib (0.14 g, 0.5 mmol), acetylacetone (1 ml) and BF_3 etherate (30 mg, 0.26 mmol). (A smaller amount of the etherate than in the synthesis *via* method B is used in order to avoid extensive polymerization.) Yield 0.11 g (85%); mp 310°C (acetonitrile).

E. Mixture of Ia (0.48 g, 2.5 mmol), $ZnCl_2$ (0.68 g, 5.0 mmol) and acetylacetone (1 g, 10 mmol) is heated on an oil bath at 190°C for 30 min. Aqueous ammonia (12 ml, 25%) is added to the cooled reaction mixture and thoroughly stirred. The crystalline precipitate is filtered off and washed with ammonia and water. Yield 0.48 g (74%); mp 310°C (acetonitrile).

F. Mixture of Ib (0.55 g, 2.0 mmol), $ZnCl_2$ (0.54 g, 4.0 mmol) and acetylacetone (0.8 g, 8 mmol) is heated on an oil bath at 180°C for 40 min. Aqueous ammonia (10 ml, 25%) is added to the cooled mixture and thoroughly stirred. The crystalline precipitate is filtered off and washed with ammonia and water. Yield 0.25 g (48%); mp 310°C (acetonitrile).

1,3-Dimethyl-7,9-diphenlpyrimido[4',5':4,5]pyrrolo[1,2-*b*]pyridazine-2,4(1H,3H)-dione (XIII). Compound Ia (0.3 g, 1.55 mmol) and dibenzoylmethane (III, 0.38 g, 1.7 mmol) are dissolved with heating in acetonitrile (10 ml). The solution is treated dropwise with BF_3 etherate (0.22 g, 1.55 mmol) and boiled for 1 h. Water (1 ml) is added after the heating is turned off. The acetonitrile is distilled to 1/3 of the initial volume. More water (10 ml) is added. The solid product is a quickly hardening oil that is ground, dried, and crystallized from alcohol (light yellow needles). Yield 0.2 g (34%); mp 245-247°C. IR spectrum: 1695, 1656 cm^{-1} (CO). PMR spectrum: 8.16-7.47 (10H, m, H_{Ph}), 7.47 (1H, s, 8-H), 6.30 (1H, s, 10-H), 3.485 (3H, s, 1-CH_3), 3.33 ppm (3H, s, 3-CH_3). Found, %: C 72.54; H 4.36; N 14.22. $C_{23}H_{18}N_4O_2$. Calculated, %: C 72.24; H 4.74; N 14.65.

Attempt to Protodebrominate Acetamide XV. Boiling solution of XV [7] (0.28 g, 0.9 mmol) in acetylacetone (2 ml) is treated with BF_3 etherate (0.11 g, 1 mmol). The mixture is boiled for 10 min and cooled. The starting material is filtered off and washed with acetonitrile. Yield 0.12 g (43%); mp 220-221°C (water).

10-Bromo-1,3,7,9-tetramethylpyrimido[4',5':4,5]pyrrolo[1,2-*b*]pyridazine-2,4(1H,3H)-dione (XIV). Solution of XII (0.15 g, 0.6 mmol) in $CHCl_3$ (7.5 ml) is treated with stirring with Br_2 (0.13 g, 0.8 mmol) in $CHCl_3$ (3.8 ml). The mixture is stirred for 30 min and evaporated. The solid is treated with NaOH (5 ml, 5%). The product is filtered off and washed with water and alcohol. Yield 0.17 g (85%). Light yellow crystals with mp 229-230°C (dioxane). IR spectrum: 1690, 1660 cm^{-1} (CO). PMR spectrum: 6.65 (1H, q, J = 1.17 Hz, 8-H), 3.95 (3H, s, 1-CH_3), 3.48 (3H, s, 3-CH_3), 2.84 (3H, d, 9-CH_3), 2.57 ppm (3H, s, 7-CH_3). Found, %: C 46.52; H 3.53; Br 23.51; N 16.97. $C_{13}H_{13}BrN_4O_2$. Calculated, %: C 46.31; H 3.89; Br 23.70; N 16.62.

Attempt to Brominate XIII. Compound XIII (0.1 g, 0.26 mmol) in $CHCl_3$ (4 ml) is treated dropwise with stirring with Br_2 (54 mg, 0.34 mmol) in $CHCl_3$ (1 ml). The mixture is stirred for 40 min and evaporated. The solid is treated with NaOH (10 ml, 2%) and ground. The solid is filtered off and washed with water and alcohol. Yield 0.1 g (100%). Yellow needles from alcohol; mp 285-287°C. PMR spectrum of the compound is identical to that of XIII.

Protodebromination of XIV in Acetylacetone. Compound XIV (0.33 g, 1 mmol) is boiled in acetylacetone (6.6 ml) for 10 min. The cooled mixture is treated with acetonitrile (14 ml). The crystalline product XIV is filtered off and washed with acetonitrile. Yield 0.21 g (83%); mp 310°C (acetonitrile).

Protodebromination of XIV by Phenol. Compound XIV (0.33 g, 1 mmol) in phenol (6 g) is boiled for 10 min. The cooled mixture is treated with stirring with aqueous KOH (20%) until the finely crystalline product stops precipitating. The product is filtered off and washed with water and acetonitrile. Yield 0.23 g (92%); mp 310°C (acetonitrile).

Reimination of IXb with Subsequent Cyclization to XII. Boiling solution of IXb (0.1 g, 0.25 mmol) in acetylacetone (1.5 ml) is treated with BF_3 etherate (36 mg, 0.25 mmol). The mixture is cooled after 15 min. The resulting suspension is treated with acetonitrile (1.5 ml). After 1 h the precipitate is filtered off and washed with acetonitrile (2 ml). Yield 35 mg (54%); mp 310°C (acetonitrile).

Reimination of X with Subsequent Cyclization to XII. Boiling solution of X (0.18 g, 0.5 mmol) in acetylacetone (1 ml) is treated with BF_3 etherate (71 mg, 0.5 mmol). After 10 min the mixture is cooled. The crystallized mixture is treated with acetonitrile (3 ml). The product is filtered off and washed with acetonitrile (5-7 ml). Yield 81 mg (63%). Crystallization from acetonitrile gives yellow crystals with mp 310°C.

Attempted Cyclization of X. Boiling solution of X (0.11 g, 0.3 mmol) in dioxane (2 ml) is treated with $ZnCl_2$ (82 mg, 0.6 mmol). The mixture is boiled for 2.5 h, cooled, treated with water (2 ml) and evaporated. The solid is treated with water (20 ml). Crystals of starting X are filtered off and washed with water. Yield 35 mg (32%); mp 261-262°C (alcohol).

Attempted Cyclization of XI. Boiling solution of XI (0.11 g, 0.3 mmol) in acetylacetone (2.5 ml) is treated with BF_3 etherate (0.11 g, 0.8 mmol). The mixture is boiled for 1 h, cooled and treated with acetonitrile (3 ml). The yellow crystals of starting XI are filtered off and washed with alcohol (3-5 ml). Yield 77 mg (70%); mp 288-289°C (alcohol).

REFERENCES

1. Yu. N. Tkachenko, E. B. Tsupak, and A. F. Pozharskii, *Khim. Geterotsikl. Soedin.*, No. 8, 1131 (1995).
2. M. Somei and M. Natsume, *Tetrahedron*, **41**, 3605 (1974).
3. M. Somei, M. Matsubara, and M. Natsume, *Heterocycles*, **3**, 1142 (1975).
4. M. Somei, M. Matsubara, and M. Natsume, *Chem. Pharm. Bull.*, **23**, 2891 (1975).
5. L. Salazar, M. Espada, D. Sanz, R. M. Claramunt, I. Elguero, S. Garsia-Granda, R. Diaz, and F. Gomez-Beltram, *J. Chem. Soc. Perkin Trans. 2*, 377 (1993).
6. A. F. Pozharskii, O. V. Dyablo, A. B. Belyaev, Z. A. Starikova, and A. I. Yanobskii, *Tetrahedron*, **54**, 9677 (1998).
7. E. B. Tsupak, Yu. N. Tkachenko, and A. F. Pozharskii, *Khim. Geterotsikl. Soedin.*, No. 9, 1242 (1994).
8. W. Kirkor and J. Baranowicz, *Acta Chim.*, No. 8, 69 (1962).