SYNTHESIS OF PYRROLES FROM N-SUBSTITUTED α-AMINO KETONES

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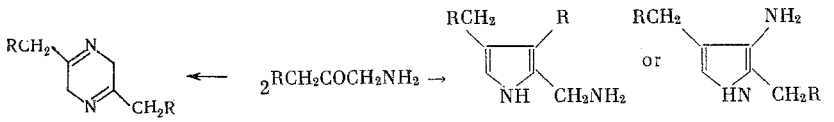
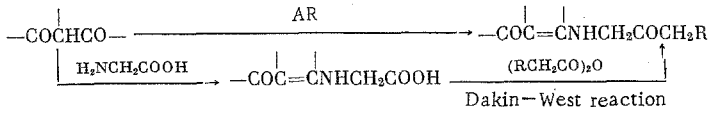
It is known [1-3] that the autocondensation of α-amino ketones (AK) to pyrroles (PL) proceeds in low yields due to the tendency of the AK to form dihydropyrazines.



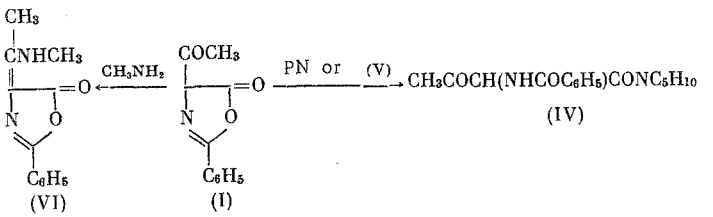
The attachment of protective groups to the nitrogen atom of the AK, which hinder the conversion of the AK to dihydropyrazines, can serve as one of the methods for increasing the yield of PL from AK. To block the nitrogen atom of the AK we examined in the present paper the possibility of preparing enamines (EN) from the AK and certain "bulky" β-dicarbonyl compounds (DC) by the direct condensation of the AK with the DC, and also by the Dakin–West reaction with the EN from the DC and α-amino acids. In addition,



we investigated the conditions for the formation of PL from the N,N-disubstituted AK in the presence of a primary amine.

As the "bulky" DC we selected 2-phenyl-4-acetyl-5-oxazolinone (I) and 2-formylcyclohexanone (II), which are easily obtained in one step respectively from hippuric acid (III) [4] and cyclohexanone [5]. The EN can be formed from (I) only in the case where the exocyclic CO group of (I) will react with the amine.

In view of the absence of data on the structural direction and conditions for the amination of (I) we studied the reaction of (I) with piperidine (PN) and CH_3NH_2. It proved that the aminolysis of (I) using PN leads to a cleavage of the azlactone ring and the formation of the piperidide of α-benzamidoacetoacetic acid (IV). The latter is also obtained by the transamination reaction of (I) with 1-piperidinocyclohexene (V).



In contrast, CH_3NH_2 reacts with (I) predominantly at the exocyclic CO group to give enamine (VI). The presence of the $CH_3C(NHCH_3)=C\diagup\diagdown$ grouping in the (VI) molecule was confirmed by the oxidative cleavage of (VI) with H_2O_2 to $CH_3CONHCH_3$. The oxidation of the related enamine (VII), formed by the reaction of (III) with $POCl_3$ and $(CH_3)_2NCHO$ by the Vilsmeier reaction, with H_2O_2 proceeds in a similar manner with

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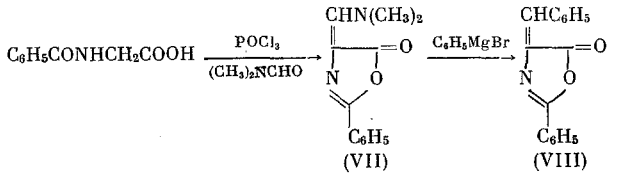
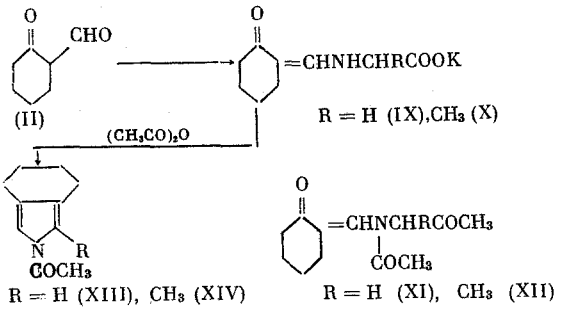
the formation of $(CH_3)_2NCHO$. The structure of (VII) follows from its ability to react with C_6H_5MgBr on the type of 1,4-addition with the formation of 2-phenyl-4-benzylidene-5-oxazolinone (VIII).

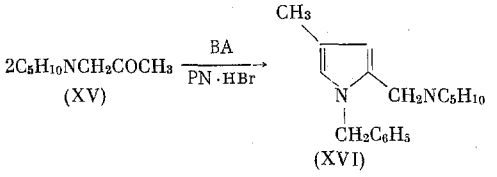


Despite the established possibility of obtaining the EN from (I), attempts to synthesize the corresponding EN from aminoacetone and glycine (or its salts) gave negative results. Attempts to condense the AK with (II) also proved unsuccessful. At the same time, (II) manifests the ability to react with the K salts of glycine and α-alanine to give enamines (IX) and (X). The exocyclic position of the nitrogen atoms in molecules (IX) and (X) was assumed on the basis of the literature data regarding the structural direction of the amination of (II) [6, 7], and was confirmed by the transformations to PL described below.

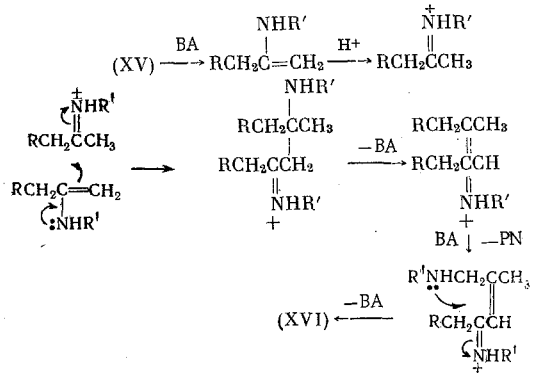


In order to obtain the N-substituted AK and study their autocondensation to PL we subjected enamines (IX) and (X) to the action of $(CH_3CO)_2O$ under the conditions of the Dakin–West reaction [4]. The reaction of (IX) and (X) with $(CH_3CO)O_2$ proceeds with noticeable speed at >100°C, and is accompanied by the evolution of CO_2. However, instead of the desired AK (XI) and (XII), the N-acylpyrroles (XIII) and (XIV) are formed as the result of the cyclization and decarboxylation of (IX) and (X). A similar synthesis of the PL was accomplished earlier from the EN of sarcosine [7].

Negative results were also obtained when N,N-dialkyl protection of the nitrogen atom of the AK was employed. Under the influence of benzylamine (BA) and PN hydrobromide, one of the members of the N,N-disubstituted AK, namely piperidinoacetone (XV), changes to 1-benzyl-2-(piperidinomethyl)-4-methylpyrrole (XVI) in ~40% yield

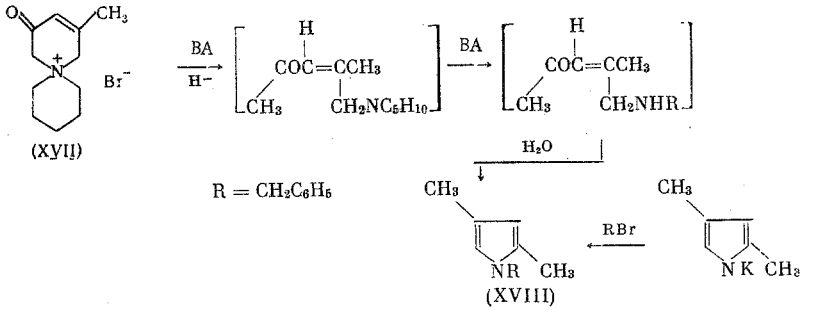


The transformation of (XV) to (XVI) apparently includes the intermediate steps of forming the EN, its dimerization, and transformation by the scheme:



$R = C_5H_{10}N$, $R' = C_6H_5CH_2$

The quaternary salt of 3-keto-2, 3, 1, 6-tetrahydropyridine (XVII), which can be regarded as being a N, N-disubstituted AK derivative, reacts with BA to give 1-benzyl-2, 4-dimethylpyrrole (XVIII), probably with involvement of the reductive cleavage reaction with hydride transfer, transamination, and cyclization according to the scheme:



(XVII) (XVIII)

The structure of (XIII), (XIV), (XVI) and (XVIII) was proved by the elemental analyses, the Ehrlich tests and the NMR spectra, and in the case of (XVIII) also by counter synthesis from 2, 4-dimethylpyrrole-potassium and $C_6H_5CH_2Br$.

EXPERIMENTAL METHOD

Piperidide of α-Benzamidoacetoacetic Acid (IV). A mixture of 0.8 g of 2-phenyl-4-acetyl-5-oxazolinone (I) [4] and 0.4 g of PN was heated for 30 min at 145-150° (bath temperature), after which it was cooled, treated with ether, and the precipitate was filtered and washed with ether. We obtained 0.42 g (50%) of (IV), mp 150-152° (from n-heptane). R_f 0.54 (here and subsequently TLC, Silufol UV_{254}, 1 : 2 acetone–benzene, detection of spots with I_2 vapors and in UV light). Ultraviolet spectrum (taken on a Specord UV-VIS instrument in alcohol): λ_{max} 226 nm (ε 10800). Infrared spectrum (taken on a UR-10 instrument with KBr, ν, cm^{-1}): 1625-1655 (CON<), 1725 ($COOC_2H_5$), 3335 (NH). NMR spectrum (taken on a DA-60-IL instrument in pyridine with HMDS, δ, ppm, singlet signals): 1.23 ($-(CH_2)_3-$), 2.13 (CH_3CO), 3.37 (CH_2NCH_2). Found: C 67.09; H 6.24; N 10.00%. $C_{16}H_{18}N_2O_3$. Calculated: C 67.13; H 6.31; N 9.79%. A mixture of 0.2 g of (I) and 0.16 g of (V) was heated at 145-150° for 30 min and the obtained (IV) was isolated the same as described above. The yield of (IV) was 0.12 g (43%).

Enamine (VI). A mixture of 1.5 g of (I) and 15 ml of 25% aqueous CH_3NH_2 solution was kept at 20° for 120 h, after which the precipitate was filtered, washed with water, and dried in the air. We obtained 0.86 g (54%) of (VI), mp 139-140 and 146-147° (from a 1 : 2 benzene–n-heptane mixture), yield 0.45 g (28%), R_f 0.46 (1 : 3 acetone–benzene). Ultraviolet spectrum: λ_{max} 235 and 350 nm (ε 13100 and 43500). Found: C 66.41; H 5.54; N 12.85%. $C_{12}H_{12}N_2O_2$. Calculated: C 66.65; H 5.56; N 12.95%. The oxidation of (VI) with excess H_2O_2 (30 min, 80-90°) gave $CH_3CONHCH_3$.

Enamine (VII). With stirring and cooling in ice, to 18 g of $(CH_3)_2NCHO$ was added a solution of 10 ml of $POCl_3$ in 30 ml of benzene, the mixture was kept at ~20° for 12 h, and then, with vigorous stirring and cooling in ice, 8.1 g of (III) was added in 15 min, after which the mixture was stirred for another 4 h at ~20°, poured on ice, and the precipitate was filtered, washed with water, and dried in the air. We obtained 9.1 g (93%) of (VII), mp 157-159° and 161-162° (from a benzene–n-hexane mixture), R_f 0.45 (Stahl silica gel, 4 : 1 benzene–acetone). Ultraviolet spectrum: λ_{max} 240 and 355 nm (ε 11580 and 35300). Found: C 66.36; H 5.67; N 12.95%. $C_{12}H_{12}N_2O_2$. Calculated: C 66.70; H 5.50; N 12.95%. The oxidation of (VII) with excess H_2O_2 (2 h, 80-90°) gave $(CH_3)_2NCHO$.

To a solution of C_6H_5MgBr (from 0.18 g of Mg and 0.7 ml of C_6H_5Br) in 10 ml of absolute THF was added 0.65 g of (VII) in portions, and the mixture was refluxed for 1 h, evaporated, and treated with water and dilute HCl solution. The reaction product was extracted with benzene. After removal of the solvent the residue was dissolved in a mixture of ether and n-hexane, and cooled to −70°. The precipitate was filtered and washed with alcohol. We obtained 0.45 g (60%) of 2-phenyl-4-benzylidene-5-oxazolinone (VIII), mp 164-165° (from benzene), the mixed melting point of which with an authentic specimen [8] was not depressed.

1-Acetyl-3,4-tetramethylenepyrrole (XIII). A mixture of the K salt of glycine (from 2.18 g of glycine and 1.68 g of KOH) and 3.16 g of 2-formylcyclohexanone (II) [5] in 25 ml of alcohol was refluxed for 3.5 h after which it was cooled, and the precipitate was filtered, washed with alcohol, and dried in the air. We obtained 3.1 g of enamine (IX). Ultraviolet spectrum: λ_{max} 315 nm. A mixture of 0.8 g of (IX) and 8 ml of $(CH_3CO)_2O$ was refluxed for 2 h, after which it was evaporated and the residue was extracted with ether. After removal of the solvent the reaction product was chromatographed on an Al_2O_3 (II activity) column. Elution with ether gave 0.25 g (42%) of (XIII) as an oil, R_f 0.25 (benzene). Ultraviolet spectrum: λ_{max} 260 nm. Infrared spectrum ($CHCl_3$): 1710 cm^{-1} (CO). NMR spectrum (CCl_4, δ, ppm): 1.60 ($-CH_2CH_2-$, multiplet); 2.25 (CH_3CO, singlet); 2.43 ($2CH_2C=C$, multiplet); 6.75 (H_2 and H_5, singlet). Found: C 73.24; H 8.27; N 8.76%. $C_{10}H_{13}NO$. Calculated: C 73.62; H 7.97; N 8.58%.

1-Acetyl-2-methyl-3,4-tetramethylenepyrrole (XIV). A mixture of the K salt of α-alanine (from 0.95 g of α-alanine and 0.06 g of KOH) and 1.36 g of (II) in 25 ml of alcohol was refluxed for 3.5 h, after which it was evaporated, 20 ml of $(CH_3CO)_2O$ was added to the residue, the mixture was refluxed for 2 h, evaporated again, and the residue was extracted with benzene. After removal of the solvent the residue was chromatographed on Al_2O_3 (II activity). Elution with ether gave 0.22 g of (XIV as an oil, R_f 0.57 [Al_2O_3 (II activity), benzene]. Ultraviolet spectrum: λ_{max} 252 nm. Infrared spectrum (as a film): 1710 cm^{-1} (CO). Found: C 74.36; H 8.80; N 8.36%. $C_{11}H_{15}NO$. Calculated: C 74.57; H 8.47; N 7.91%.

1-Benzyl-2-(piperidinomethyl)-4-methylpyrrole (XVI). A mixture of 0.62 g of piperidinoacetone (XV) [9], 0.47 g of benzylamine and 0.73 g of PN hydrobromide in 10 ml of absolute benzene was refluxed for 7 h, after which the precipitate was filtered, the mother liquor was evaporated, and the residue was extracted with ether. After removal of the solvent the reaction product was chromatographed on an Al_2O_3 (II activity) column. Elution with ethyl acetate gave 0.2 g (35%) of (XVI) as an oil, R_f 0.39 [Al_2O_3 (II activity), 1:1 heptane–benzene]. NMR spectrum (CCl_4, δ, ppm): 1.33 ($-(CH_2)_3-$, multiplet); 1.94 (CH_3, singlet); 2.20 ($-CH_2NCH_2-$, multiplet); 3.09 ($-CH_2N<$, singlet); 5.00 ($C_6H_5CH_2N<$, singlet); 5.63 (H_3, doublet); 6.50 (H_5, multiplet); 7.05 (C_6H_5, multiplet). Found: C 80.56; H 8.82; N 10.13%. $C_{18}H_{24}N_2$. Calculated: C 80.65; H 8.95; N 10.45%.

1-Benzyl-2,4-dimethylpyrrole (XVIII). In known manner [10], starting with bromoacetone and (XV), we obtained the quaternary salt (XVII), mp ~250° (decompn.). Ultraviolet spectrum: λ_{max} 233 nm (ε 11800). Infrared spectrum: 1680 cm^{-1} (C=O). A mixture of 0.5 g of (XVII) and 2 ml of BA was heated at 135-140° for 1 h, after which the excess BA was removed by vacuum-distillation with xylene, and the residue was chromatographed on an Al_2O_3 (II activity) column. Elution with benzene gave 0.17 g (50%) of (XVIII) as an oil, R_f 0.80 (1:1 acetone–benzene). Ultraviolet spectrum: λ_{max} 209 nm. NMR spectrum (CCl_4, δ, ppm): 1.94 ($2CH_3$, singlet); 4.75 (CH_2, singlet); 5.50 and 6.08 (H_3 and H_5, singlets); 7.00 (C_6H_5, multiplet). Found: C 84.41; H 8.06; N 7.50%. $C_{13}H_{15}N$. Calculated: C 84.44; H 8.10; N 7.57%.

A mixture of 2,4-dimethylpyrrolepotassium (from 0.4 g of 2,4-dimethylpyrrole [11] and 0.16 g of K) and 0.72 g of $C_6H_5CH_2$ Br in 4 ml of absolute benzene was kept at 20° for 5 h, after which it was refluxed for 3.5 h, the precipitate was filtered, and the residue was chromatographed as described above. We obtained 0.13 g of impure (XVIII), which had the same R_f and the signals of the protons in the NMR spectrum as sample (XVIII), which had been synthesized from (XVII) and BA.

CONCLUSIONS

1. The reaction of 2-phenyl-4-acetyl-2-oxazolinone with piperidine and methylamine respectively gave the piperidide of α-benzamidoacetoacetic acid and 2-phenyl-4-(α-methylaminoethylidene)-5-oxazolinone.

2. Reaction of the enamines, obtained by the reaction of the K salts of glycine and α-alanine with 2-formylcyclohexanone, with acetic anhydride leads to the formation of 1-acetyl-3,4-tetramethylenepyrrole and its 2-methyl derivative.

3. The reaction of piperidinoacetone with benzylamine and piperidine hydrobromide in benzene gives 1-benzyl-2-(piperidinomethyl)-4-methylpyrrole.

4. The quaternary salt of 3-keto-2,3,1,6-tetrahydropyridine is converted to 1-benzyl-2,4-dimethylpyrrole under the influence of benzylamine.

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