CONDENSATION OF 2-AMINO-3-CYANO-4,5,6,7-TETRAHYDROINDOLE WITH β-DICARBONYL COMPOUNDS

M. V. Mezentseva,
A. N. Grinev, O. S. Anisimova,
L. M. Alekseeva, and Yu. N. Sheinker.

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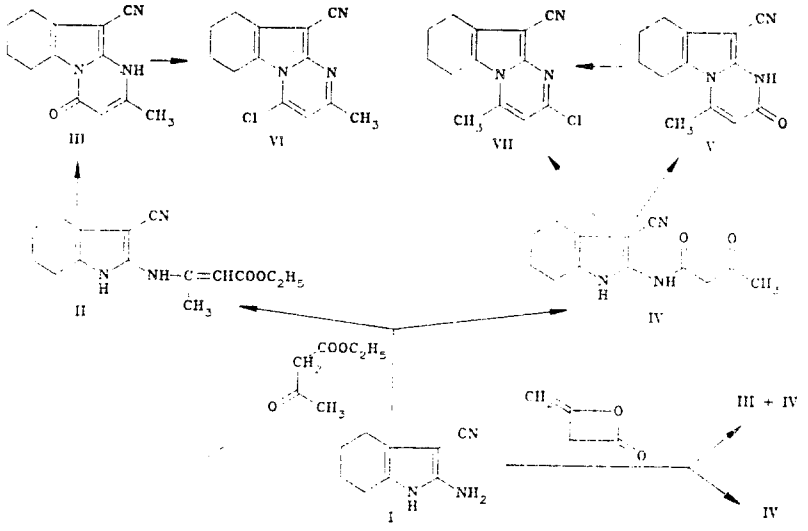
Depending on conditions, the condensation of 2-amino-3-cyano-4,5,6,7-tetrahydroindole with β-dicarbonyl compounds leads to 2-methyl-4-oxo- or 4-methyl-2-oxo-10-cyano-6,7,8,9-tetrahydropyrimido[1,2-a]indoles via the intermediate compounds: 2-(3-ethoxy-carbonyl-prop-2-en-2-yl amino) and 2-(1,3-dioxobutylamino)-3-cyano-4,5,6,7-tetrahydroindoles, respectively.

Continuing our investigations on the synthesis of condensed heterocyclic systems containing pyrrole and indole fragments [1-3], we studied the condensation of 2-amino-3-cyano-4,5,6,7-tetrahydroindole (I) with acetoacetic ester and diketene.

It is known that reactions of this type are highly dependent on the prevailing conditions and do not always proceed unequivocally (see, for example, [4, 5].)

In fact, the reaction of amine I with acetoacetic ester leads to isomeric compounds 2-methyl-4-oxo-10-cyano-6,7,8,9-tetrahydropyrimido[1,2-a]indole (III) and 4-methyl-2-oxo-10-cyano-6,7,8,9-tetrahydropyrimido[1,2-a]indole (V), depending on the structure of the intermediates formed: 2-(3-ethoxycarbonylprop-2-en-2-ylamino)-3-cyano-4,5,6,7-tetrahydroindole (II) and 2-(1,3-dioxo-butylamino)-3-cyano-4,5,6,7-tetrahydroindole (IV), respectively.



The determining factor in the formation of crotonate II or amide IV is the temperature of the reaction. Thus, for example, at 100°C with an excess of acetoacetic ester, crotonate II is mainly obtained, while under more rigorous conditions (140°C), amide IV is formed. When catalytic amounts of concentrated hydrochloric acid are added, or when the reaction is carried out in glacial acetic acid, the formation of the crotonate, which proceeds even at room temperature, is considerably accelerated. A similar influence of the reaction conditions on the reaction of acetoacetic ester with aminopyridines [6] and aminopyrazoles [7], has been observed previously. The patterns of behavior of amine I in the reaction with acetoacetic ester that we found are similar to those described in the literature [8].

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The presence in the PMR spectrum of crotonate II of broadened signals of the NH group protons (9.86 and 8.76 ppm) and also of the vinyl proton (4.76 ppm) indicates that an enamine and not an imine structure is realized for this compound. In the mass spectrum of compound II, a peak of the molecular ion (273)* is observed, the main path of the fragmentation of which involves the elimination of the C_2H_5OH molecule. The fragment F formed (227) possibly has a cyclic structure, which coincides with the structure of compound III. This is indicated by the coincidence of the futher fragmentation of ion F and the molecular ion of compound III.

In the IR spectrum of compound IV there are two bands at 1685 and 1725 cm^{-1} of the amide and ketonic carbonyl. Signals are observed in the PMR spectrum at 10.11 and 10.14 (NH), 3.63 (VH_2) and 2.21 ppm (CH_3CO). The presence of 1,3-dioxobutyl grouping in the molecule of IV is also confirmed by the fragmentation sequence of the molecular ion. Ion peaks are observed in the mass spectrum corresponding to the elimination from M^+ (245) of a molecule of acetone (187) and an O=C=CH-CO-CH_3 fragment (161), as well as of the acetyl cation (43). Further decomposition of ion 161 practically coincides with the fragmentation of compound I.

When crotonate II is heated to 150°C, 4-oxopyrimidine III is formed, while boiling of amide IV in acetic acid results in 2-oxo-pyrimidine V. In the IR spectra of the isomeric oxo compounds a difference is observed in the position of the absorption of the NH and C=O groups: for the 4-oxo form, the bands are in the 3180...3350 region (NH) and at 1730 (C=O), while for the 2-oxo form, they are in the 3270...3530 region (NH) and at 1675 cm^{-1} (C=O), which agrees with the data in [4, 9].

The 2-oxo- and 4-oxo forms also differ in their absorption in the UV region. For the 2-oxo form, a hypsochromic shift of the absorption maxima in comparison with the absorption of the 4-oxo form is characteristic, which can also be used for the determination of the isomeric forms.

In the PMR spectra, the signals of the methyl group protons and the 3-H proton in the 2-oxo form (2.60 and 5.88 ppm) are shifted to the weaker field, while the signals of the NH and 6-H protons (12.25 and 2.96 ppm) are shifted to the stronger field relative to the signals of the corresponding protons of the 4-oxo from (2.23, 5.40, 12.42 and 3.05 ppm).

The mass spectra of the isomeric compounds III and V are characterized by an intense peak of the moelcular ion (227) and a general character of the fragmentation, in which the main path is the elimination of C_2H_4 from the cyclohexane ring with the formation of the (199†) fragment. The spectra of the isomers differ in the ratio of the peak intensities of several fragments. A distinct feature of the mass spectrum of compound III is the presence of the [M-$NCCH_3$] fragment (186), while in the spectrum of the isomeric compound V the [M-CONH] ion (184) is observed instead. The presence of peaks of these ions in the spectra makes it possible to distinguish the structure of the oxopyrimidine ring. It should be noted that the elimination of the $NCCH_3$ group from the M^+ in the case of compound III, probably indicates the fragmentation of this compound from the hydroxy form of the molecular ion.

When amine I is heated with diketene in either chloroform or acetic acid at 40-80°C, amide IV is formed preferentially. Further increase in temperature (95-114°C, in acetic acid) leads to the cyclization of this amide into 2-oxopyrimidoindole V, while boiling of amine I with diketene in benzene leads to a mixture of 4-oxopyrimidoindole III and amide IV. The yield of the compounds formed depends on the duration of heating and degree of dilution of the solution. Thus, when the reaction is carried out in a dilute solution (1:125), compound III‡ is formed in 64% yield. Increase in the concentration of the reagents (1:12.5) leads to a decrease in the yield of compound III (29%) and to an increase in the yield of amide (IV) (57%).

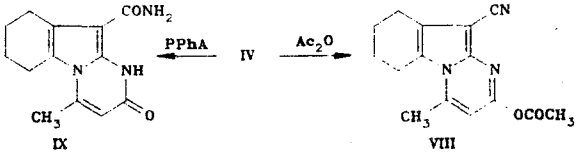
The lack of depression of the melting point of a mixed sample, the coincidence of the R_f values, IR and the UV spectra of compounds III and V obtained during the condensation of amine I with acetoacetic ester or diketene show that they are identical.

It is clear tht diketene acylates both the exocyclic amino group and the cyclic nitrogen atom, as has been observed previously for aminopyridines also [5].

*Here and below, the values of m/z are given for ion peaks.
†A similar fragmentation is characteristic for compound I.
‡In UV light, 4-oxopyrimidine III has a brightblue fluorescence in contrast to the nonfluorescing isomer V.

The action of phosphorus oxychloride on compounds III-V results in the formation of 2-methyl-4- (VI) and 4-methyl-2-chloro-10-cyano-6,7,8,9-tetrahydropyrimido[1,2-a]indole (VII), respectively.

When heated with acetic anhydride, compounds IV and V convert into 2-acetyloxy-4-methyl-10-cyano-6,7,8,9-tetrahydropyrimido[1,2-a]indole (VIII), while with polyphosphoric acid, 2-oxo-4-methyl-10-carbamoyl-6,7,8,9-tetrahydropyrimido[1,2-a]indole (IX) is formed.



IX VIII

In the IR spectra of compound VIII, the stretching vibration bands in the 3100-3500 region (NH) and at 1685 cm^{-1} (C=O) disappear, and an absorption band appears at 1785 cm^{-1} ($OCOCH_3$), while in compound IX, the vibration band of the C≡N group at 2100 cm^{-1} disappears, and stretching vibration bands of the NH and NH_2 groups and of the C=O group appear at 1650, 1670 cm^{-1}.

In the mass spectrum of compound VIII, a peak of the molecular ion (269) is observed, the main fragmentation of which involves the elimination of the $COCH_2$ group. The subsequent fragmentation of the $[M - COCH_2]^+$ ion (227) coincides practically completely with the spectrum of compound IV. The molecular ion of compound IX has a mass number 245, which corresponds to the proposed structure. The frgmentation of the molecular ion of IX involves a stepwise elimination of the amide group; $[M - NH_3]^+$ (228). $[M - NH_3 - CO]^+$ (200), with subsequent splitting of C_2H_4 from the cyclohexane ring (ion 172).

EXPERIMENTAL

The IR spectra were run in mineral oil on a Perkin-Elmer 457 spectrophotometer, the UV spectra in alcohol on an EPS-3 spectrophotometer, and the PMR spectra in solutions in DMSO-D_6 on a Jeol-C-60 HL spectrometer, using TMS as internal standard. The mass spectra were obtained on a Varian MAT-112 mass-spectrometer with a ionizing voltage of 70 eV. The course of the reactions and the purity of the compounds obtained were monitored chromatographically by carrying out TLC on Silufol UV-254 plates in a benzene-ethyl acetate, 3:2, system, with development in UV light and by iodine vapor. The spectral characteristics of the synthesized compounds are given in Table 1. The data of the elemental analysis for C, H, N (Cl) correspond to the calculated values.

2-Amino-3-cyano-4,5,6,7-tetrahydroindole (1) was obtained according to a method described in [2].

2-(3-Ethoxycarbonylprop-2-en-2-ylamino)-3-cyano-4,5,6,7-tetrahydroindole (II), $C_{15}H_{19}N_3O_2$). A. A mixture of 1.61 g (10 mmoles) of amine I and 5 ml of acetoacetic ester was heated to 100°C and then held for 4 h at this temperature. The mixture was cooled, the precipitate that separated out was filtered and dried. Yield. 1.2 g (44%) of compound II, mp 156-157°C (from alcohol).

B. A 2 ml portion of acetioacetic ester was added to a suspension of 1.61 g (10 mmoles) of amine 1 in 6 ml of glacial acetic acid. The mixture was stirred for 30 min at 20°C. The precipitate was filtered and dried. Yield, 1.8 g (66%) of compound II.

C. Two drops of concentrated HCl were added to a suspension of 1.61 g (10 mmoles) of amine I in 5 ml of acetoacetic ester. The reaction mixture was allowed to stand for 3 h (20°C). The precipitate was filtered, washed with water, and dried. Yield, 2 g (73%) of compound II.

Samples of compound II, obtained by methods B and C did not show depression of the melting point of a mixed sample with a sample obtained by method A, and had the same R_f values.

2-Methyl-4-oxo-10-cyano-6,7,8,9-tetrahydropyrimido[1,2-a]indole (III, $C_{13}H_{13}N_3O$). A. A mixture of 1.61 g (10 mmoles) of amine I and 5 ml of acetoacetic ester was slowly heated to 140°C and then held at this temperature for 2 h. The reaction mixture was cooled, the precipitate was filtered and dried. Yield, 1.1 g (50%) of compound III, mp 294-296°C (from methanol).

B. A 2 ml portion (28 mmoles) of diketene was added dropwise, with stirring, to a solution of 1.61 g (10 mmoles) of amine I in 200 ml of benzene, and the mixture was boiled for 8 h. The precipitate that separated was filtered. The yield of compound III was 1.560 g (64%).

TABLE 1. Characteristics of Compounds II-IX Synthesized

Compound	IR spectrum, cm^{-1}	UV spectrum, λ max, nm (log ε)	Mass spectrum	PMR spectrum, ppm
II	3225 (NH); 2220 (C≡N); 1660 (C=O); 1600 (C=C)	288 (4,12)	274 (5), 273 (30), 272 (7), 228 (23), 227 (100), 226 (16), 200 (20), 199 (77), 198 (12), 187 (5), 186 (16), 185 (11), 184 (6), 171 (13), 160 (7), 159 (16), 158 (8), 157 (19), 143 (6), 137 (7), 116 (5), 105 (3), 67 (8)	1,2 (3H, t, CH_3, J=7 Hz); 1,76 (4H, t, 5,6-CH_2); 1,93 (3H, s, CH_3); 2,50 (4H, t, 4,7-CH_2); 4,06 (2H, q, OCH_2); 4,76 (H, s, CH); 8,76 (H, s, 2-NH); 9,86 (H, s, 1-NH)
III	3350, 3260, 3180 (NH); 2210 (C≡N); 1730 (C=O); 1690, 1625 (C=C, C=N)	232 (4,4), 285 (4,0), 335 (3,9)	228 (13), 227 (60), 226 (26), 200 (14), 199 (100), 186 (4), 171 (5), 160 (6), 158 (11), 157 (7), 143 (5), 133 (13), 116 (6), 91 (3), 67 (7), 40 (8)	1,71 (4H, m, 7,8-CH_2); 2,23 (3H, s, CH_3); 2,50 (2H, m, 9-CH_2); 3,05 (2H, m, 6-CH_2); 5,40 (H, s, 3-CH); 12,42 (H, br. s, NH)
IV	3340, 3260, 3180 (NH); 2210 (C≡N); 1725, 1680 (C=O)	295 (4,09)	246 (5), 245 (25), 188 (3), 187 (22), 162 (12), 161 (100), 160 (26), 159 (16), 143 (4), 134 (8), 133 (90), 132 (4), 120 (4), 118 (3), 116 (4), 106 (3), 105 (7), 85 (3), 84 (4), 77 (3), 69 (5), 65 (4), 43 (25), 40 (10)	1,5 (4H, m, 5,6-CH_2); 2,21 (3H, s, CH_3); 2,45 (4H, m, 4,7-CH_2); 3,63 (2H, s, CH_2); 10,11 (1H, br. s, 2-NH); 10,14 (H, s, 1-NH)
V	3510, 3360, 3280 (NH); 2210 (C≡N); 1685 (C=O); 1610 (C=C)	220 (4,3), 253 sh (4,5), 260 (4,6), 280 sh (4,2)	228 (13), 227 (82), 226 (22), 200 (12), 199 (100), 198 (12), 184 (4), 171 (5), 170 (5), 160 (7), 143 (3), 133 (6), 116 (3), 84 (3), 67 (22,4)	1,72 (4H, m, 7,8-CH_2); 2,50 (2H, m, 9-CH_2); 2,60 (3H, d, 4CH_3, J=0,9Hz); 2,96 (2H, m, 6-CH_2); 5,88 (H, q, 3-CH)
VI	2200 (C≡N), 1610 (C=C, C=N)	215 (4,6), 220 sh (4,6), 236 sh (4,6), 242 (4,6), 261 (4,6), 270 (4,6), 270 sh (3,8), 303 (4,0), 315 (3,9), 375 (3,8)	247 (20), 246 (16), 245 (62), 244 (20), 219 (29), 218 (16), 217 (100), 216 (14), 204 (3), 181 (4), 180 (4), 167 (3), 122 (3), 88 (3), 66 (5)	1,8 (3H, q, 2-CH_3); 2,47...2,52 (4H, m, 7,8-CH_2); 2,7 (2H, m, 9-CH_2); 3,31 (2H, m, 6-CH_2); 7,1 (H, s, 3-CH)
VII	2200 (C≡N), 1610 (C=C, C=N)	215 (4,6), 220 sh (4,6), 236 sh (4,6), 242 (4,6), 261 (4,6), 270 (4,7), 290 sh (3,9), 303 (4,0), 315 (3,9), 375 (3,8)	247 (23), 246 (18), 245 (74), 244 (22), 219 (37), 218 (25), 217 (100), 216 (22), 182 (4), 181 (6), 180 (7), 167 (5), 143 (3), 142 (3), 116 (5), 67 (6), 41 (3)	2,49...2,53 (4H, m, 7,8-CH_2); 2,86 (3H, s, 4-CH_3); 3,29 (2H, m, 9-CH_2), 3,32 (2H, m, 6-CH); 6,84 (H, s, 3-CH)
VIII	2205 (C≡N), 1780 ($OCOCH_3$), 1625 (C=C, C=N)	198 (4,3), 220 (4,6), 240 (4,6), 258 (4,6), 266 (4,6), 296 (4,0), 298 (3,9), 370 (3,8)	269 (4), 228 (14), 227 (100), 226 (19), 200 (10), 199 (70), 198 (8), 184 (4), 170 (5), 160 (6), 133 (4), 67 (17)	1,80...1,93 (4H, q, 7,8-CH_2); 2,3 (3H, s, OCH_3); 2,80 (2H, t, 9-CH_2); 2,82 (3H, t, 4-CH_3); 6,31 (H, s, 3CH)
IX	3100, 3200 (NH); 1670, 1650 (C=O)	206 sh (4,5), 222 (4,6), 260 sh (4,6), 268 (4,7), 290 (4,2)	246 (14), 245 (78), 229 (18), 228 (100), 227 (10), 218 (5), 217 (4), 211 (8), 200 (27), 199 (16), 188 (3), 174 (4), 173 (6), 172 (36), 171 (9), 162 (6), 161 (3), 160 (4), 159 (4), 158 (7), 144 (3), 143 (8), 134 (4), 133 (4), 130 (3), 118 (4), 116 (4), 68 (5), 67 (16)	

Samples of compound III, obtained according to method A and B had identical IR and UV spectra.

2-(1,3-Dioxobutylamino)-3-cyano-4,5,6,7-tetrahydroindole (IV, $C_{13}H_{15}N_3O_2$). A. A suspension of 1.61 g (10 mmoles) of amine I in 5 ml acetoacetic ester was submerged in a silicone bath, preliminarily heated to 150°C. The compound dissolved at 120°C, and a precipitate began to separate out at 140°C. The mixture was held at this temperature for 10 min, was then cooled, the precipitate was filtered and washed with methanol. Yield, 1.76 g (72%), mp 230-232°C (from methanol).

B. Diketene (2.32 ml) was added at 40°C in one portion, with stiriring, to a solution of 1.61 g (10 mmoles) of amine I in 20 ml of glacial acetic acid. The precipitate began to separate at 60°C, The reaction mixture was heated to 80°C, cooled, the precipitate was filtered, washed with water and methanol. The yield of compound IV was 1.6 g (66%).

2-Oxo-4-methyl-10-cyano-6,7,8,9-tetrahydropyrimido[1,2-a]indole (V, $C_{13}H_{13}N_3O$). A. A mixture 1.6 g (10 mmoles) of amine I, 20 ml of glacial acetic acid and 2.3 ml of diketene was boiled for 2 h. The precipitate that separated out was filtered, washed with methanol, and dried. The yield of compound V was 1.73 g (76%), mp 302-304°C (from MeOH–DMFA).

B. A. suspension of 1.2 g (5 mmoles) of amide IV in 10 ml of glacial acetic acid was boiled for 1 h. The precipitate was washed with water and methanol. Yield, 0.88 g (80%).

2-Methyl-4-chloro-10-cyano-6,7,8,9-tetrahydropyrimido[1,2-a]indole (VI, $C_{13}H_{12}ClN_3$). A suspension of 3.5 g (15 mmoles) of pyrimidoindole III in 29.2 g (17.5 ml) of freshly distilled phosphorus oxychloride was heated to dissolution and the solution was allowed to stand at room temperature for 1 h. It was then poured onto ice, the precipitate was filtered, washed with water and acetone. After recrystallization from acetone, 1.7 g (45%) of compound VI, mp 224-226°C (from acetone) was obtained.

4-Methyl-2-chloro-10-cyano-6,7,8,9-tetrahydropyrimido[1,2-a]indole (VII, $C_{13}H_{12}ClN_3$). A. Under the conditions of the synthesis of compound VI, from 0.43 g (2 mmoles) of pyrimidoindole V and 3 ml of phosphorus oxychloride, 0.23 g (50%) of compound VII was obtained, mp 282-284°C (from dioxane).

B. Compound VII was obtained in a similar way from 1.6 g (6 mmoles) of amide IV and 15 ml of phosphorus oxychloride, yield 1 g (62%).

2-Acetoxy-4-methyl-10-cyano-6,7,8,9-tetrahydropyrimido[1,2-a]indole (VIII, $C_{15}H_{15}N_3O_2$). A. A syspension of 0.5 g (2 mmoles) of amide IV in 5 ml of acetic anhydride was boiled for 1 h, then cooled, and poured into water. The precipitate was filtered and washed with water. Yield, 0.5 g (93%) of compound VIII, mp 235-236°C (from alcohol).

B. compound VIII was obtained by the same method from 0.5 g (2 mmoles) of pyrimidoindole V and 5 ml of acetic anhydride. Yield 0.5 g (85%).

2-Oxo-4-methyl-10-carbamoyl-6,7,8,9-tetrahydropyrimido[1,2-a]indole (IX, $C_{13}H_{15}N_3O_2$). A suspension of 1 g (4 mmoles) of amide IV in polyphosphoric acid, obtained from 8.4 g of phosphoric anhydride and 4 ml of phosphoric acid, was heated with stirring for 2 h at 110-120°C. The mixture was then poured into water and neutralized with ammonia. The precipitate was filtered and washed with water. Yield, 0.8 g (74%) of compound IX, mp 345-347°C (from acetic acid).

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