REACTION OF 1-AMINO-, 2-AMINO-, AND 1,2-DIAMINOIMIDAZOLES WITH β-DIKETONES

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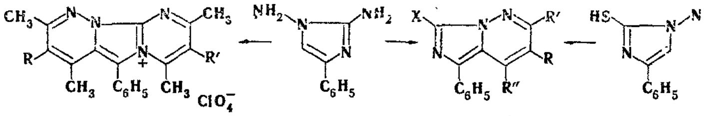
1,2-Diamino-4-phenylimidazolium perchlorate condenses with 2 mole of β-diketones to give pyrimido[2',1':2,3]imidazo[1,5-b]pyridazinium derivatives, while, like 1-amino-2-mercapto-4-phenylimidazole, to give imidazo[1,5-b]pyridazine derivatives. Salts of 1-benzylideneamino- and 1-(2-thiazolyl)-2-aminoimidazoles react with β-diketones to give substituted imidazo[1,2-a]pyrimidinium derivatives.

A three-ring pyrimidoimidazopyridazinium perchlorate (IIa) was unexpectedly obtained in the reaction of 1,2-diamino-4-phenylimidazolium perchlorate [1] with acetylacetone. Compound IIa is formed very readily even in the cold in alcohol solution. Both methyl groups of the pyrimidine ring of IIa are active and form a bisstyryl with p-dimethylaminobenzaldehyde.



II a-c I IV a-i III

IVa–d X=NH$_2$; IVe, g; X=SH; IVf X=SCH$_3$; IVh X=NHC(CH$_3$)CHCOCH$_3$; IVi X==N(COCH$_3$)$_2$; IVa,c–g, IIa (R'=R) R=H; IIb (R'=R), IIc IVb R=C$_2$H$_5$; IIc R'=H; IVa,b,e,f,h,i, R'=R''=CH$_3$; IVc,g R'=R''=C$_6$H$_5$; IVd R'=CH$_3$, R''=C$_6$H$_5$

The methyl groups in the 4 and 7 positions have the lowest chemical shifts in the PMR spectrum of IIa (2.00 and 1.65 ppm) because of shielding by the phenyl group (7.26 ppm). The signals of these groups are split (J = 0.7 and 1.2 Hz) due to coupling with the 3-H protons (6.99 ppm) and 8-H (6.52 ppm) protons, respectively, in contrast to the methyl groups in the 2 and 9 positions (2.48 and 2.22 ppm). The coupling of the 7-CH$_3$ protons with 8-H and of the 4-CH$_3$ protons with 3-H is confirmed not only by the mutual splitting with identical constants but also by the double-proton resonance when, for example, the peak at 2.00 ppm is narrowed as the signal at 6.99 ppm is saturated. Other β-diketones also give salts of the II type.

1,2-Diamino-2-phenylimidazole (I) reacts with β-diketones in acetic acid to give imidazopyridazines (IVa-d), which give II on reaction with β-diketones in the presence of mineral acids. Thus IVb, which reacts with acetylacetone in the presence of HClO$_4$ to give IIc, is obtained by condensation of I with 3-ethyl-2,4-pentanedione. Compound IVa reacts with acetic anhydride to give a diacetyl derivative at the amino group (IVi); this was also observed for starting amine I [1].

As in the spectra of II, the 5-phenyl signal in the PMR spectra of imidazopyridazines (IV) is not split, and 4-CH$_3$ is shielded by the phenyl group and is split by coupling with 3-H. However, all of the signals in the spectrum of IVa are shifted diamagnetically as compared with the corresponding signals of cation II, except for the 4-CH$_3$ signal, which is shifted to weak field by 0.1 ppm. This can be explained by the lower shielding of the methyl group by the phenyl group in IV as compared with II, in which the phenyl group is more noncoplanar because of additional coupling with 4-CH$_3$. When R'' = Ph in IV, the phenyl groups in the 4 and 5 positions shield one another and give one overall signal at 6.5 ppm, while when R'' = CH$_3$, the phenyl group in the 5 position gives a signal at 7.12 ppm.

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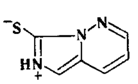
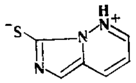
The condensation with β-diketones to give imidazo[1,5-b]pyridazines is apparently characteristic for 1-aminoimidazoles. Thus 1-amino-2-mercapto-4-phenylimidazole [2] reacts with β-diketones in the presence of mineral acids to give IVe, g; when the components are heated in the absence of acid they give a noncyclic azomethine, which is cyclized by the action of acids. Of the possible structures of the 7-mercapto derivatives (IVe,g), the most significant ones, at least in the solid state, are probably the α and β structures, inasmuch as a number of intense bands at 2600-3050 cm^{-1}, which are characteristic for $\nu\overset{+}{N}-H$, are observed in the IR spectrum (in KBr).



α



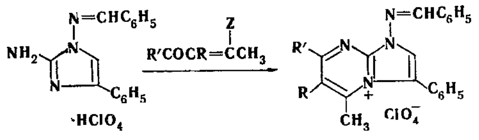
β

A mixture of isomers is formed in the reaction of benzoylacetone with I. The PMR spectrum of the crude product contains the signals of two methyl groups, the intensity ratio of which gives a ratio of 5 : 1 for isomers IVd and IV ($X=NH_2$, $R=H$, $R'=C_6H_5$, $R''=CH_3$). The first isomer (IVd) was obtained after recrystallization.

Compound IVe reacts with dimethyl sulfate in alkaline media to give a methylthio derivative (IVf), which is subsequently methylated at $N_{(6)}$ to give a quaternary salt. The $2\text{-}CH_3$ and 3-H signals in the PMR spectrum of the quaternary salt are shifted by 0.1-0.15 ppm to weak field as compared with the analogous signals of IV, while the phenyl signal was virtually unchanged, and the $4\text{-}CH_3$ signal is shifted to strong field by ~ 0.1 ppm. If the methylation had occurred at $N_{(1)}$, all of the signals should have been shifted to weak field. The methyl group attached to $N_{(6)}$ removes the phenyl group even more from the plane of the two-ring system, and its signal therefore does not change, despite conversion of the system to a cation, while the chemical shift of $4\text{-}CH_3$ becomes even smaller because of an increase in the shielding of this group by the phenyl group.

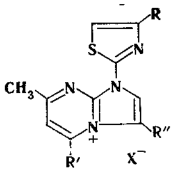
A product of the reaction with two molecules of acetylacetone, to which we assigned anil structure IVh, was also obtained in the reaction of I with acetylacetone in the absence of mineral acids or in acetic acid or trifluoroacetic acid.

To confirm the structure of II we used 2-amino-1-benzylideneamino-4-phenylimidazole perchlorate (V) [1], which gives salts VIa, b on condensation with acetylacetone and 3-chloro-2-methyl-2-butenal.



V

VI a-b



VII a-d

VIa $R=H$. $R'=CH_3$, $Z=OH$; VIb $R=CH_3$, $R'=H$, $Z=Cl$; VIIa—c $X=ClO_4$; VIId $X=$ $=CF_3COO$; VIIa $R=R'=CH_3$, $R''=C_6H_5$; VIIb $R=R''=C_6H_5$, $R'=CH_3$; VIIc $R=R'=R''=$ $=C_6H_5$; VIId $R=R''=p\text{-}BrC_6H_4$, $R'=CH_3$

The formation of a pyrimidine ring is confirmed by the fact that salts VIa, b give polymethine dyes and their PMR spectra correspond to the spectra of II. As with other heterocycles [3], 3-chloro-2-methyl-2-butenal in this case gives one isomer (VIb) with an unsubstituted γ postion of the pyrimidine ring with respect to the bridge nitrogen atom. However, we were unable to hydrolyze the azomethines and obtain 1-amino derivatives by means of 2-amino-1-(α-methylbenzylideneamino)-4-phenylimidazole, inasmuch as this compound is hydrolyzed so readily that three-ring systems II are formed immediately.

Imidazo[1,2-a]pyrimidinium salts with alkyl substituents attached to $N_{(1)}$ can be obtained by alkylation of imidazo[1,2-a]pyrimidines [4, 5], but compounds with more complex substituents attached to $N_{(1)}$ cannot be obtained by this method. The latter are readily accessible via the above-described condensation. Thus salts of 1-(2-thiazolyl)-2-amino-4-arylimidazoles react with β-diketones to give imidazo[1,2-a]pyrimidinium salts (VII) with 2-thiazolyl substituents attached to $N_{(1)}$. Salts VII give polymethine dyes, and their structures were confirmed by their PMR spectra. The methyl group in the 5 position is shielded by the phenyl group in the 3 position, and its chemical shift is 2.07 ppm, which is characteristic for a fragment of this type [7]. The structure of VIIc, obtained by condensation with benzoylacetone, was proved by the fact that the signal of one methyl group (2.70 ppm), which determines its position as $7\text{-}CH_3$, is observed in its PMR spectrum. In addition, a convincing proof of the position of the phenyl group (5-C_6H_5) is its coupling with 3-C_6H_5, as a result of which (mutual shielding) the signals of both phenyl groups are shifted to strong field (6.72 and 6.78 ppm as against 7.31 for 3-C_6H_5 in VIIa).

EXPERIMENTAL

The PMR spectra of trifluoroacetic acid solutions of the compounds relative to hexamethyldisiloxane (HMDS) as the internal standard were recorded with a ZKR-60 spectrometer.

2,4,7,9-Tetramethyl-6-phenylpyrimido[2',1':2,3]imidazo[1,5-b]pyridazinium Perchlorate (IIa). A) A solution of 0.69 g (2.5 mmole) of the perchlorate of I and 1.5 ml (15 mmole) of acetylacetone in 3 ml of alcohol was refluxed for 2 h, after which it was worked up to give 0.57 g (57%) of a light-yellow crystalline precipitate of IIa, which was crystallized from methanol. It exploded on heating above 330° without melting. Found: Cl 8.9; N 14.3%. $C_{19}H_{19}ClN_4O_4$. Calculated: Cl 8.8; N 14.0%.

B) When 0.69 g of the perchlorate of I and 2 ml of acetylacetone were heated on a water bath, 0.74 g (74%) of IIa precipitated from the hot reaction mixture after 5-7 min.

7,9-Dimethyl-6-phenyl-2,4-bis(p-dimethylaminostyryl)pyrimido[2',1':2,3]imidazo[1,5-b]pyridazinium Perchlorate. A 0.1-g (0.25 mmole) sample of IIa was dissolved by heating in 2 ml of acetic anhydride, after which 0.15 g (1 mmole) of p-dimethylaminobenzaldehyde and two drops of triethylamine were added, and the mixture was heated at 170-175° for 3 h. The mixture was cooled, and the resulting precipitate was washed with boiling alcohol to give 0.05 g (30%) of a bisstyryl with mp 283-285°. Found: Cl 5.5; N 12.6%. $C_{37}H_{37}ClN_6O_4$. Calculated: Cl 5.5; N 12.8%.

2,4,7,9-Tetramethyl-3,8-diethyl-6-phenylpyrimido[2',1':2,3]imidazo[1,5-b]pyridazinium Perchlorate (IIb). A mixture of 0.69 g (2.5 mmole) of the perchlorate of I and 0.9 ml (7 mmole) of 3-ethyl-2,4-pentanedione was heated at 150-160° for 3 h. The resulting dark mass was triturated with acetone to give 0.37 g (32%) of a brown powder. The product was crystallized from ethanol to give yellow crystals of perchlorate IIb with mp 244-246°. PMR spectrum, δ, ppm: 0.83 (CH_2CH_3), 1.60 (7-CH_3), 2.03 (4-CH_3), 2.30 (9-CH_3), 2.53 (2-CH_3), 2.2-2.5 (CH_2CH_3), 7.27 (C_6H_5). Found: Cl 8.0; N 12.2%. $C_{23}H_{27}ClN_4O_4$. Calculated: Cl 7.7, N 12.2%.

2,4,7,9-Tetramethyl-8-ethyl-6-phenylpyrimido[2',1':2,3]imidazo[1,5-b]pyridazinium Perchlorate (IIc). A mixture of 0.27 g (1 mmole) of IVb, 0.5 g (5 mmole) of acetylacetone, and a few drops of 57% perchloric acid was heated at 160-170° for 2 h, and the resulting dark mass was triturated with ether and crystallized from alcohol to give 0.15 g (35%) of yellow crystals of IIc with mp 256-257° (from ethanol); PMR spectrum, δ, ppm: 0.78 (CH_2CH_3), 1.66 (7-CH_3), 1.97 (4-CH_3), 2.24 (CH_2CH_3), 2.32 (9-CH_3), 2.49 (2-CH_3), 7.01 (3-H), 7.31 (6-C_6H_5). Found: Cl 8.2; N 13.2%. $C_{21}H_{23}ClN_4O_4$. Calculated: Cl 8.2; N 13.0%.

7-Amino-2,4-dimethyl-5-phenylimidazo[1,5-b]pyridazine (IVa). A solution of 0.52 g (3 mmole) of diamine I in 1 ml of acetic acid and 0.4 ml (4 mmole) of acetylacetone was heated on a water bath for 2 h, after which the mixture was cooled and poured into water. The aqueous mixture was made alkaline with ammonia and worked up to give 0.46 g (65%) of orange crystals of IVa with mp 213° (from ethanol). PMR spectrum, δ, ppm: 1.75 (4-CH_3), 2.03 (2-CH_3), 6.05 (3-H), 7.15 (5-C_6H_5). Found: C 70.7; H 5.8; N 23.5%. $C_{14}H_{14}N_4$. Calculated: C 70.5; H 5.9; N 23.6%. Treatment of the filtrate with a 20% NaOH solution gave 0.2 g (28%) of yellow crystals of 7-(4-oxo-2-penten-2-ylamino)-2,4-dimethyl-5-phenylimidazo[1,5-b]pyridazine (IVh) with mp 217-219° (from ethanol). Found: C 69.9; H 6.0; N 17.6%. $C_{19}H_{20}N_4O_2$. Calculated: 71.3; H 6.2; N 17.5%. Treatment of IVh with perchloric acid gave a perchlorate that was identical to IIa.

7-(Diacetylamino)-2,4-dimethyl-5-phenylimidazo[1,5-b]pyridazine (IVi). A mixture of 0.12 g (5 mmole) of IVa and 0.3 ml (3 mmole) of acetic anhydride was heated on a water bath for 30 min, after which 0.12 g of the diacetyl derivative was removed by filtration. Water was added to the filtrate to give another 0.03 g of the diacetyl derivative. The overall yield of IVi with mp 162-163° (from ethanol) was 94%. Found: C 67.1; H 5.8; N 17.3%. $C_{18}H_{18}N_4O_2$. Calculated: C 67.4; H 5.6; N 17.4%.

7-Amino-2,4-dimethyl-3-ethyl-5-phenylimidazo[1,5-b]pyridazine (IVb). This compound was obtained from I and 3-ethyl-2,4-pentanedione by refluxing in acetic acid at 150-160° for 2 h. The yield of product with mp 215-216° (from ethanol) was 40%. Found: C 71.6; H 6.2; N 21.2%. $C_{16}H_{18}N_4$. Calculated: C 72.2; H 6.8; N 21.0%.

7-Amino-2,4,5-triphenylimidazo[1,5-b]pyridazine (IVc). A mixture of 0.7 g (4 mmole) of I and 1.56 g (7 mmole) of dibenzoylmethane in 1 ml of acetic acid was heated at 200° for 4 h, after which it was cooled, triturated with ether, and washed several times with boiling methanol to give 0.16 g (12%) of a red substance with mp 252-255° (from propanol). PMR spectrum, δ, ppm: 6.77 (4- and 5-C_6H_5), 7.18 and 7.57 (three and two protons of 2-C_6H_5, respectively). Found: C 79.3; H 5.2; N 15.7%. $C_{24}H_{18}N_4$. Calculated: C 79.5; H 5.0; N 15.5%.

7-Amino-2-methyl-4,5-diphenylimidazo[1,5-b]pyridazine (IVd). This compound was obtained by heating I and benzoylacetone in acetic acid at 175-180° for 2 h. The mixture was triturated with ether and methanol to give a ruby-red crystalline substance with mp 275° (from propanol) in 76% yield. PMR spectrum, δ, ppm: 2.17 (2-CH_3), 6.20 (3-H), 6.66 (4- and 5-C_6H_5). Found: C 76.1; H 5.7; N 18.6%. $C_{19}H_{16}N_4$. Calculated: C 76.0; H 5.4; N 18.7%.

7-Mercapto-2,4-dimethyl-5-phenylimidazo[1,5-b]pyridazine (IVe). A 0.47-g (2.5 mmole) sample of III was heated at 135-140° for several minutes with 2 ml of acetylacetone in the presence of a few drops of 57% perchloric acid. The resulting precipitate was separated and washed with ether to give 0.54 g (83%) of yellow crystals of IVe with mp 309-311° (from ethanol). PMR spectrum, δ, ppm: 1.87 (4-CH_3), 2.20 (2-CH_3), 6.34 (3-H), 7.14 (5-C_6H_5). Found: N 16.4; S 12.5%. $C_{14}H_{13}N_3S$. Calculated: N 16.5; S 12.6%.

1-(4-Oxo-2-penten-2-ylamino)-2-mercapto-4-phenylimidazole. A mixture of 0.95 g (5 mmole) of III and 2 ml (20 mmole) of acetylacetone was heated at 150°. The mixture began to solidify after 10 min, and it was then triturated with ether to give 1.31 g (95%) of a white crystalline substance with mp 223-224° (from ethanol). Found: N 15.6; S 11.4%. $C_{14}H_{15}N_3OS$. Calculated: N 15.4; S 11.7%.

7-Methylthio-2,4-dimethyl-5-phenylimidazo[1,5-b]pyridazine (IVf). A 0.1-g (0.9 mmole) sample of dimethyl sulfate was added to a solution of 0.1 g (0.4 mmole) of IVe in 15 ml of 2% NaOH, and the mixture was worked up to give 0.08 g (75%) of a yellow precipitate of IVf with mp 169-170° (from ethanol). Found: N 15.6; S 11.9%. $C_{15}H_{15}N_3S$. Calculated: N 15.6; S 11.9%.

7-Methylthio-2,4,6-trimethyl-5-phenylimidazo[1,5-b]pyridazinium Perchlorate. A solution of 0.4 g (1.5 mmole) of IVf in 2 ml of dimethylformamide (DMF) was heated with 0.6 ml (5.4 mmole) of dimethyl sulfate on a water bath for 2.5 h. The resulting salt was precipitated with ether, dissolved in water, and isolated as the perchlorate. The shiny white plates [0.54 g (96%)] had mp 225-226° (from methanol). PMR spectrum, δ, ppm: 1.75 (4-CH_3), 2.30 and 2.43 (2-CH_3 and S-CH_3), 3.60 (6-CH_3), 6.47 (3-H), 7.17 (5-C_6H_5). Found: Cl 9.2; S 8.3%. $C_{16}H_{18}ClN_3O_4S$. Calculated: Cl 9.4; S 8.4%.

7-Mercapto-2,4,5-triphenylimidazo[1,5-b]pyridazine (IVg). A mixture of 0.38 g (2 mmole) of III, 0.66 g (3 mmole) of dibenzoylmethane, a few drops of 57% perchloric acid, and 1 ml of acetic acid was heated at 120° for 2-3 min. Shiny ruby-red plates [0.67 g (88%)] with mp 315-317° (from diethylene glycol) precipitated from the resulting solution. PMR spectrum, δ, ppm: 6.83 (4- and 5-C_6H_5, broad peak), 8.43 (3-H), 7.17 and 7.70 (three and two protons of 2-C_6H_5, respectively). Found: N 11.2; S 8.7%. $C_{24}H_{17}N_3S$. Calculated: N 11.1; S 8.4%.

1-Benzylideneamino-5,7-dimethyl-3-phenylimidazo[1,2-a]pyrimidinium Perchlorate (VIa). A solution of 1.81 g (5 mmole) of V in 1 ml of acetylacetone was heated at 190-200° for 7 h, and the reaction product was triturated with ether to give 1.83 g (86%) of yellowish crystals of VIa with mp 267-268° (from methanol). PMR spectrum, δ, ppm: 1.99 (5-CH_3), 2.46 (7-CH_3), 6.90 (6-H), 7.20 (3-C_6H_5), 7.92 (2-H), 8.57 (N−CHC_6H_5), 7.55 and 7.18 (two and three protons of the benzylidene phenyl group). Found: Cl 8.4; N 13.2%. $C_{21}H_{19}ClN_4O_4$. Calculated: Cl 8.3; N 13.1%.

1-Benzylideneamino-5,6-dimethyl-3-phenylimidazo[1,2-a]pyrimidinium Perchlorate (VIb). A 0.6 ml sample of 3-chloro-2-methyl-3-butenal was added to a suspension of 0.72 g (2 mmole) of V in 10 ml of methanol in the cold, after which the mixture was allowed to stand for 3 days and was then filtered to give 0.37 g (43%) of yellowish crystals of VIb with mp 267-268° (from methanol). PMR spectrum, δ, ppm: 2.03 (5-CH_3), 2.13 (6-CH_3), 7.20 (3-C_6H_5), 8.04 (2-H), 8.55 and 8.63 (7-H and N−CHC_6H_5), 7.62 and 7.19 (two and three protons of the benzylidene phenyl group). Found: Cl 8.3; N 13.2%. $C_{21}H_{19}ClN_4O_4$. Calculated: Cl 8.3; N 13.1%.

5,7-Dimethyl-3-phenyl-1-(4-methyl-2-thiazolyl)imidazo[1,2-a]pyrimidinium Perchlorate (VIIa). A 0.36-g (1 mmole) sample of 1-(4-methyl-2-thiazolyl)-2-amino-4-phenylimidazolium perchlorate was heated with 0.3 g (3 mmole) of acetylacetone at 145° for 1 h, after which the mixture was cooled, and the reaction mass was triturated with ether and filtered to give 0.38 g (80%) of VIIa with mp 253-254° (from ethanol). Found: Cl 8.5; N 13.4%. $C_{18}H_{17}ClN_4O_4S$. Calculated: Cl 8.4; N 13.2%.

5,7-Dimethyl-3-phenyl-1-(4-phenyl-2-thiazolyl)imidazo[1,2-a]pyrimidinium Perchlorate (VIIb). This compound was similarly obtained from 1-(4-phenyl-2-thiazolyl)-2-amino-4-phenylimidazole perchlorate and acetylacetone. The yield of product with mp 280° (from nitromethane) was 91%. PMR spectrum, δ, ppm: 2.07 (5-CH_3), 2.61 (7-CH_3), 7.20-7.42 (protons of the phenyl group of the thiazole ring), 7.31 (3-C_6H_5), 7.52 (6-H and thiazole ring proton), 8.22 (2-H). Found: Cl 7.5; N 12.2%. $C_{23}H_{19}ClN_4O_4S$. Calculated: Cl 7.4; N 11.6%.

7-Methyl-3,5-diphenyl-1-(4-phenyl-2-thiazolyl)imidazo[1,2-a]pyrimidinium Perchlorate (VIIc). This compound was obtained from 1-(4-phenyl-2-thiazolyl)-2-amino-4-phenylimidazolium perchlorate and benzoylacetone by heating at 145° for 3 h. The yield of yellow crystals with mp 247-248° (from nitromethane) was 82%. PMR spectrum, δ, ppm: 2.70 (7-CH_3), 6.72 and 6.78 (3- and 5-C_6H_5), 7.24 and 7.45 (6H and thiazole ring proton), 7.08-7.31 (protons of the phenyl group of the thiazole ring), 8.19 (2-H). Found: Cl 6.7; N 10.5%. $C_{28}H_{21}ClN_4O_4S$. Calculated: Cl 6.5; N 10.3%.

5,7-Dimethyl-3-(p-bromophenyl)-1-[4-(p-bromophenyl)-2-thiazolyl]imidazo[1,2-a]pyrimidinium Trifluoroacetate (VIId). A 0.47-g (1 mmole) sample of 1-[4-(p-bromophenyl)-2-thiazolyl]-2-amino-4-(p-bromophenyl)imidazole was dissolved in 0.4 ml of trifluoroacetic acid, after which 0.2 g (2 mmole) of acetylacetone was added, and the mixture was heated at 145-150° for 1.5 h. It was then cooled, and the reaction product was triturated with ether to give 0.49 g (79%) of VIId with mp 310° (from ethanol). Found: Br 24.5; N 8.6%. $C_{25}H_{17}Br_2F_3N_4O_2$. Calculated: Br 24.5; N 8.6%.

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