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REACTIONS OF 1,2-DIAMINOBENZIMIDAZOLES WITH β-DICARBONYL COMPOUNDS

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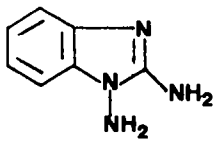
Abstract- The reactions of 1,2-diaminobenzimidazoles with β-dicarbonyl compounds give 1,2,4-triazepino [2,3-a] benzimidazole and pyrimido [1,2-a] benzimidazole-derivatives.

The commonest method of preparation of 1,5-benzodiazepines remains the reaction of o-phenylenediamines with β-dicarbonyl compounds. When o-phenylenediamines are replaced by C,N-1,2-diamino derivatives such as 1,2-diaminobenzimidazole 1, condensed 1,2,4-triazepines with a nitrogen atom at a condensation position and/or other tricyclic compounds can be obtained. We here study the reactions between 1 and several β-dicarbonyl compounds. All compounds reported, except 3a, are new.

Condensation of 1 with acetylacetone gave needles of bright orange colour. The ^{1}H-NMR spectrum ($CDCl_3$) showed besides two singlets at δ1.8 ppm (Me) and 1.9 ppm (Me), singlets at δ4.35 ppm and δ9.4 (NH) and a multiplet at δ6.9-7.4 ppm (H7-10). The signal at δ4.35 ppm can be attributed to the H3 proton of 1H, 5H or 6H tautomers of 1,2,4-triazepino [2,3-a] benzimidazole derivatives or to an equilibrium mixture between them. We propose for this product the structure 2 corresponding to the 6H tautomer because the known amidine-reactivity of 2-aminobenzazoles would explain this conjugated structure that is unusual in 1,5-benzodiazepines derivated from o-phenylenediamines and other C,N-1,2-diamines, for which all spectroscopic methods indicate the 3H-tautomer to be the most stable[1,2,3].



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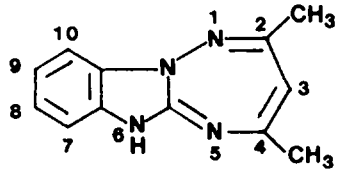

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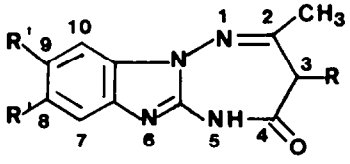
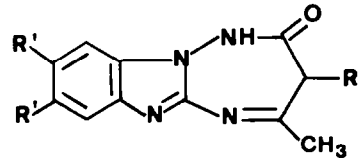
When C,N-1,2-diamines react with β-oxoesters, the nonequivalence of the amino groups is responsible for two probable pathways to form seven-membered rings. Thus, condensation of 3,4-diamino-1,2,4-triazole derivatives with ethyl acetoacetate, after some conflictive speculations[4,5] has being reported to afford the

triazolotriazepine resulting from the reaction of the hydrazine group on the ketone carbonyl group of the ketoester[6,7]. Other condensation reactions of ethyl acetoacetate and C,N-diamino heterocycles thus far studied have involved 3,4-diamine-5-oxo - 4,5 - dihydro-1,2,4-triazine derivatives, for which the same regioselective cyclization corresponding to the higher basicity of the hydrazine amine group has been also reported[8].

In our case, 1,2-diaminobenzimidazole 1, has three nucleophilic nitrogen atoms (the two amino groups and the 3-nitrogen atom). Cyclization reactions through the two amino groups with ethyl acetoacetate would give rise to the two isomeric 1,2,4-triazepino [2,3-a]benzimidazoles 3 and/or 4, while cyclizations through the 2-amino group and the 3-nitrogen atom would give the two isomer oxo-pyrimido [1,2-a]benzimidazoles 5 and/or 6. Derivatives of 1,2,4-triazolo[2,3-a] benzimidazole that would be other possible cyclization or rearrangement products have not been isolated.



3a: R=R'=H
3b: R=H; R'=CH_3
3c: R=CH_3; R'=H



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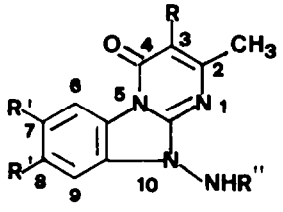
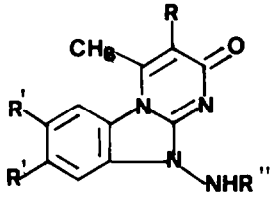




5a: R=R'=H; R''=$C(CH_3)=CHCO_2Et$
5b: R=H; R'=CH_3; R''=$C(CH_3)=CHCO_2Et$
5d: R=R'=R''=H

6

Povstyanoi et al. in a brief report[9] have described 3a as the product of the acid catalyzed reaction of 1 and ethyl acetoacetate although the structure assignment was exclusively supported on mass and IR spectroscopic data. In this context we have studied the chemical behaviour of 1 with an excess of several β-oxoesters.

The reaction of 1 with ethyl acetoacetate in a molar ratio 1:5 gave 2-methyl-3H,5H-1,2,4-triazepino [2,3-a]benzimidazol-4-one 3a in 52% yield together with 5a in 7% yield as 1:1 and 1:2 condensation products respectively. Structural analysis of 3a by ^1H and ^{13}C-NMR data and X-ray diffraction analysis confirmed its

formation through the initial attack of the N-amino group on the keto group, followed by ring closure.

^{1}H-NMR data of 3a are in accord with the 3H-tautomer. The ^{13}C-NMR assignments, although tentative, are in good agreement with those of 2-aminobenzimidazole[10] and other benzimidazole derivatives[11]. Tables 1 and 2 give the atomic parameters, the interatomic distances and angles obtained from X-ray diffraction of compound 3a and figure 1 shows the molecule and the atom-numbering used in the crystallographic study. The 1,2,4-triazepine ring shows a distorted boat conformation and localized N_3=C_2 double bond, and the benzimidazole moiety is planar in agreement with other benzimidazole compounds[12,13,14]. There are no unusual bond distances or angles in the molecule.

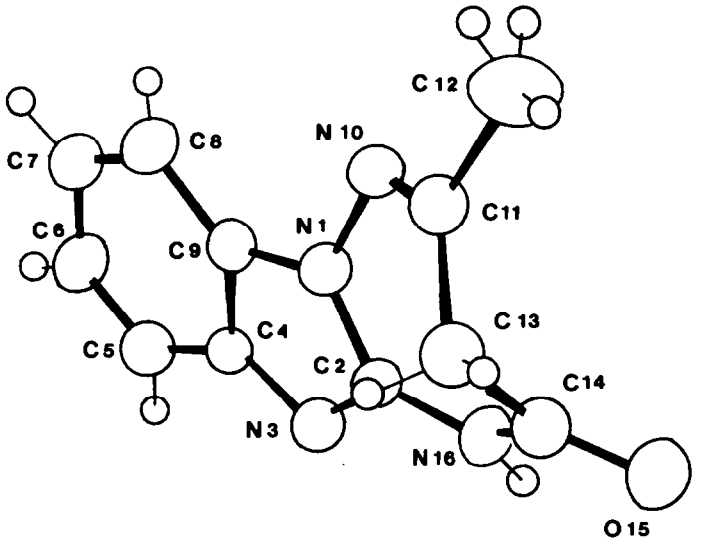


Figure 1.- A view of the molecular structure and atom-numbering of 3a.

TABLE 1.- Coordinates and thermal parameters

ATOM	x	y	z	U_{eq}*
N1	1.1666 (4)	0.1245 (1)	0.7960 (6)	39 (1)
C2	1.1220 (5)	0.0712 (2)	0.6812 (7)	36 (1)
N3	0.9973 (4)	0.0473 (1)	0.7572 (6)	42 (1)
C4	0.9533 (5)	0.0866 (2)	0.9295 (7)	39 (1)
C5	0.8308 (5)	0.0826 (2)	1.0691 (8)	46 (1)
C6	0.8147 (6)	0.1289 (2)	1.2272 (9)	53 (2)
C7	0.9166 (6)	0.1776 (2)	1.2478 (9)	55 (2)
C8	1.0406 (6)	0.1820 (2)	1.1127 (9)	48 (2)
C9	1.0555 (5)	0.1352 (2)	0.9530 (7)	39 (1)
N10	1.2671 (4)	0.1684 (1)	0.7342 (6)	44 (1)
C11	1.3993 (6)	0.1514 (2)	0.6707 (8)	45 (1)
C12	1.5034 (11)	0.1970 (3)	0.5813 (16)	76 (2)
C13	1.4551 (6)	0.0896 (2)	0.6674 (9)	44 (1)
C14	1.3456 (5)	0.0566 (2)	0.4580 (7)	43 (1)
O15	1.3924 (4)	0.0386 (1)	0.2703 (6)	55 (1)
N16	1.1898 (4)	0.0483 (2)	0.4888 (6)	42 (1)

*U_{eq}= (1/3). $\Sigma(u_{ij}.a_i^*.a_j^*.a_i.a_j.\cos(a_i,a_j))x10^3$

TABLE 2.

Bond distances (Å)

N1 -C2	1.389 (5)	N1 -C9	1.437 (6)
N1 -N10	1.425 (5)	C2 -N3	1.364 (6)
C2 -N16	1.397 (6)	N3 -C4	1.401 (5)
C4 -C5	1.437 (7)	C4 -C9	1.425 (6)
C5 -C6	1.385 (7)	C6 -C7	1.425 (7)
C7 -C8	1.433 (8)	C8 -C9	1.397 (6)
N10-C11	1.338 (6)	C11-C12	1.532 (10)
C11-C13	1.503 (6)	C13-C14	1.529 (6)
C14-O15	1.235 (6)	C14-N16	1.431 (6)

Bond angles

C9 -N1 -N10	123.1 (3)	C2 -N1 -N10	130.8 (3)
C2 -N1 -C9	104.1 (3)	N1 -C2 -N16	122.3 (3)
N1 -C2 -N3	113.3 (3)	N3 -C2 -N16	124.2 (4)
C2 -N3 -C4	106.7 (3)	N3 -C4 -C9	107.9 (4)
N3 -C4 -C5	129.9 (4)	C5 -C4 -C9	122.2 (4)
C4 -C5 -C6	116.9 (4)	C5 -C6 -C7	120.5 (5)
C6 -C7 -C8	123.4 (4)	C7 -C8 -C9	115.6 (4)
C4 -C9 -C8	121.3 (4)	N1 -C9 -C8	130.7 (4)
N1 -C9 -C4	108.0 (3)	N1 -N10-C11	118.1 (3)
N10-C11-C13	125.6 (4)	N10-C11-C12	119.4 (4)
C12-C11-C13	115.0 (5)	C11-C13-C14	108.4 (4)
C13-C14-N16	117.5 (4)	C13-C14-O15	120.0 (4)
O15-C14-N16	122.5 (4)	C2 -N16-C14	126.9 (3)

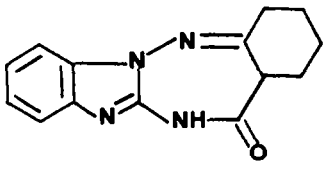
Some torsion angles

C9 -N1 -N10-C11	156.0 (4)	C2 -N1 -N10-C11	-42.7 (6)
N10-N1 -C2 -N16	8.3 (6)	N1 -C2 -N16-C14	31.0 (6)
N3 -C2 -N16-C14	-155.8 (4)	N16-C2 -N3 -C4	-172.9 (4)
N1 -N10-C11-C12	174.8 (5)	N1 -N10-C11-C13	-2.4 (6)
N10-C11-C13-C14	66.5 (6)	C12-C11-C13-C14	-110.8 (5)
C11-C13-C14-O15	113.8 (4)	C11-C13-C14-N16	-65.7 (5)
C13-C14-N16-C2	5.7 (6)	O15-C14-N16-C2	-173.8 (4)

The structure assignment of compound 5a was based on the chemical shift of the H6 proton in its ^{1}H-NMR spectrum. This proton resonates 1.21 ppm downfield respect to the aromatic protons H7-9. If the tricyclic compound under consideration has the 4-oxo structure as in a 5-derivative, one would expect the H6 proton to be shifted downfield from the main aromatic signals by the paramagnetic anisotropic effect of the carbonyl at C4 as it is indeed the case. Other pyrimido [2,1-b] benzazol-4-one derivatives prepared by condensation of 2-amino-benzazoles and dimethyl 2-aminofumarate or diethyl ethoxymethylenemalonate, and used as starting

materials to interesting antiallergic agents[15], have been distinguished from pyrimido[2,1-b]benzazol-2-one derivatives type 6, prepared with dimethyl acetylendicarboxylate, using the same criterion[T6]. Because of the free rotation about the N10-NH hydrazine bond the "peri" effect of the N10 substituent in either isomer would be negligible.

An analogous behaviour has been observed in the condensation of 1 with ethyl 2-oxocyclohexane carboxylate, which afforded the tetracyclic derivatives 7 (37% yield) and 8 (4% yield) and in the reaction of 5,6-dimethyl-1,2-diaminobenzimidazole with ethyl acetoacetate which gave 3b and 5b.



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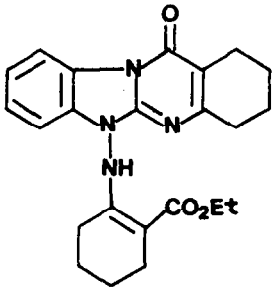

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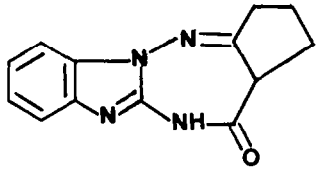

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Only the main condensation products 3c and 9 were characterized in the reactions of 1 with ethyl 2-methyl-3-oxobutyrate and ethyl-2-oxocyclopentane carboxylate respectively. All spectroscopic and analytical data are according to the proposed structures. In the case of compound 9 the CH_2 protons in the ^{1}H-NMR spectrum appear divided into two types in the ratio 3:3 probably due to the carbonyl anisotropic effect.

Formation of compounds 5 and 8 must occur through the initial condensation of the C-amino group with the keto-carbonyl group of the β-oxoesters, the final ring closure taking place at the N-3 imidazole nitrogen atom. Further condensation of the N-amino group only occurs in the above mentioned reaction conditions, with a large excess of β-ketoesters. When the reaction of 1 with ethyl acetoacetate was performed equimolecularly in refluxing toluene, 3a was obtained in 12% yield with traces of 2-methyl-10-amino-10H-pyrimido[1,2-a]benzimidazol-4-one 5d, which were detected by ^{1}H-NMR (δvalues in ppm from TMS, DMSO-d_6, 200 MHz): H-6 (8.42,d), H-7,8,9 (7.4-7.6, m), H-3 and NH_2 (5.95, two overlapped singlets) and CH_3 (2.33, s).

EXPERIMENTAL

Melting points are uncorrected and were measured with a Buchi capillary melting point apparatus. IR spectra were recorded on a Perkin-Elmer 577 spectrophotometer and NMR spectra with a Perkin-Elmer R24-B (60 MHz), a Bruker WP-80-SY (20 MHz) and a Brucker WM-200-SY (200 MHz) spectrometers (shifts in ppm relative TMS). UV Spectra were recorded in methanol (10^{-5} and 10^{-6}M solutions) on a spectrophotometer Bausch and Lomb Spectronic 2000 between 500 and 200 nm.

Reactions of 1,2-diaminobenzimidazole with β-dicarbonyl compounds. General procedure: A mixture of 1 mmol of the corresponding 1,2-diaminobenzimidazole[17] and 5 mmol of the β-dicarbonyl compound was refluxed with stirring for 1 hour. Any precipitated solid was collected by filtration and recrystallized. The secondary products were isolated from the mother liquors in some cases and were also recrystallized.

2,4-Dimethyl-6H-1,2,4-triazepino[2,3-a]benzimidazole (2) Crystals from ethanol (91%); mp 192-195°C; IR(KBr): 3600-2500 (N-H), 1670 and 1630 (C=N, C=C) cm^{-1}. UV λ_{max} MeOH (log ε) 304, 277, 256, 241, 218 nm (3.70, 4.28, 4.15, 4.15, 4.61); ^{1}H-NMR δ(60MHz, $CDCl_3$) 1.8 (3H, s, Me-2 or 4), 1.9 (3H, s, Me-4 or 2), 4.35 (1H, s, H-3), 6.9-7.4 (4H, m, aromatic protons), 9.4 (1H, ws, NH). Found: C 67.97; H 5.80; N 26.77. Calc. for $C_{12}H_{12}N_4$: C 67.90; H 5.69; N 26.39%.

2-Methyl-3H,5H-1,2,4-triazepino[2,3-a]benzimidazol-4-one (3a) Pale yellow crystals from methanol (52%); mp 290-293°C; (lit, 281-282°C (from DMF)); IR (KBr): 3500-2500 (very complex broad absorption including νNH stretching vibrations), 1695 (C=O), 1635 and 1580 (C=N, C=C) cm^{-1}. UV λ_{max} MeOH (log ε) 292, 282, 244, 206 nm (4.02, 4.02, 4.27, 4.47); ^{1}H-NMR δ(200 MHz, DMSO-d_6) 2.33 (3H, s, Me-2), 3.60 (2H, s, H-3), 7.18-7.28 (2H, m, H-8,9), 7.46 (1H, m, H-7 or 10), 7.51 (1H, m, H-10 or 7), 11.6 (1H, ws, NH). ^{13}C-NMR δ(20 MHz, DMSO-d_6) 165 (C-4), 161 (C-5a), 142.9 (C-6a), 138.3 (C-2), 132.8 (C-10a), 123.0 (C-9), 121.7 (C-8), 110.1 (C-10), 117.5 (C-7), 42.7 (C-3, superimposed to DMSO), 24.7 (CH_3). Found: C 61.60; H 4.34; N 25.82. Calc. for $C_{11}H_{10}N_4O$: C 61.66; H 4.7; N 26.15%.

X-ray structure analysis of (3a): A prismatic crystal of about 0.1x0.2x0.3 mm, was mounted along the long axis. Intensities were measured with an Enraf-Nonius CAD-4 four circle diffractometer graphite monochromated. The cell dimensions were refined from 35 reflections with the Bragg angle θmax<30°.
Crystal data, $C_{11}H_{10}N_4O$, M=214.2, $P2_1/c$, a= 8.833 (1), b=22.939 (2), c=5.374 (1) Å, β=101.52 (1)°, V=1011.6 (1) $Å^3$, Z=4, Dx=1.334g/cm^3, λ(MoK α)=0.7107 Å (graphite monochromator), μ=7.086 cm^{-1}, F(000)=448, R=0.059, Rw=0.061.
Intensity data were obtained for 1725 reflections, of which 1138 were considered as observed with Rint=0.002. Reflections for -9<h<9, 0<k<26, 0<l<6 were collected with the w-2θ scan technique and corrections were made for Lorentz and polarization effects. Two standard reflections were monitored with less than 0.5% intensity variation. No absorption correction was made.
Structure was solved by MULTAN 76[18] and refined by full-matrix, least-squares procedures, with anisotropic temperature factors on the non-H atoms. Hydrogen atoms were localized by difference Fourier synthesis and isotropically refined. The function minimized was $w(\Sigma|Fo|-|Fc|)^2$ with w, from the empirical weighting scheme fit to give no trends in $\langle w\Delta^2F\rangle$vs. $\langle Fo\rangle$or$\langle \sin\theta/\lambda\rangle$. The atomic scattering factors and anomalous dispersion coefficients are taken from International Tables for X-Ray Crystallography[19]. Refinement of 185 parameters ($I>2\sigma(I)$) converged at R=0.059, Rw=0.061 and S=3.43. Residual electron density in final difference map 0.12 $eÅ^{-3}$, Δ/ρ =0.02.
The assimmetry parameters from Cremer and Pople[20] are: q_2=0.769 (4), q_3=0.240 (4), ϕ_2=52.8 (3), ϕ_3=-93.5 (9), QT=0.805 (4), θ_2=72.7 (3).
The computations were performed on a XRAY76 System[21] using MULTAN 76[18], PESOS[22] programs on a VAX11/750 computer.

2,8,9-Trimethyl-3H,5H-1,2,4-triazepino[2,3-a]benzimidazol-4-one (3b) Crystals from ethanol (54%); mp 297-299°C dec.; IR(KBr): 3500-2500 (N-H), 1695 (C=O), 1635 and 1590 (C=N, C=C)cm^{-1}. UV λ_{max} MeOH (log ε) 298, 288, 249, 205 nm (4.11, 4.04, 4.29, 4.56); ^{1}H-NMR δ(200 MHz, DMSO-d_6) 2.31 (3H, s, Me-8 or 9), 2.33 (3H, s, Me-2), 2.37 (3H, s, Me-9 or 8), 3.54 (2H, s, H-3), 7.24 (1H, s, H-7 or 10), 7.27 (1H, s, H-10 or 7), 11.5 (1H, ws, NH). Found: C 64.75; H 6.21; N 23.39. Calc. for $C_{13}H_{14}N_4O$: C 64.44; H 5.82; N 23.12%

2,3-Dimethyl-3H,5H-1,2,4-triazepino[2,3-a]benzimidazol-4-one (3c) Crystals from ethanol (60%); mp 225-228°C; IR(KBr): 3100-2500 (N-H), 1700 (C=O), 1630 and 1585 (C=N, C=C) cm^{-1}. UV λ_{max} MeOH (log ε) 291, 282, 249, 228, 204 nm (3.92, 3.92, 4.24, 4.26, 4.48). ^{1}H-NMR δ(60 MHz, $CDCl_3$) 1.5 (3H, d, Me-3), 2.3 (3H, s, Me-2) 3.5 (1H, q, H-3), 7.2-7.6 (4H, m, aromatic protons), 11.7 (1H, ws, NH). Found: C 63.18; H 5.55; N 24.52. Calc. for $C_{12}H_{12}N_4O$: C 63.14; H 5.29; N 24.54%.

2,3-Tetramethylene-3H,5H-1,2,4-triazepino[2,3-a]benzimidazol-4-one (7) Crystals from methanol (37%); mp 279-282°C dec.; IR(KBr): 3600-2500 (N-H), 1695 (C=O), 1620 and 1590 (C=N, C=C) cm^{-1}. UV λ_{max} MeOH (log ε) 287, 282, 253, 206 nm (3.94, 3.99, 4.29, 4.53); ^{1}H-NMR δ(200 MHz, DMSO-d_6) 1.4-1.6 (6H, m) and 2.7-2.9 (2H, m), 3.75 (1H, m, H-3), 7.24 (2H, m, H-8,9), 7.50 (2H, m, H-7,10), 10.39 (1H, ws, NH). Found: C 66.03; H 5.89; N 22.17. Calc. for $C_{14}H_{14}N_4O$: C 66.12; H 5.54; N 22.03%.

2,3-Trimethylene-3H,5H-1,2,4-triazepino[2,3-a]benzimidazol-4-one (9) Crystals from methanol (13%); mp 280-283°C; IR(KBr): 3500-2500 (N-H), 1695 (C=O), 1660 and 1630 (C=N, C=C) cm^{-1}. UV λ_{max} MeOH (log ε) 291, 281, 254, 209 nm (3.94, 4.01, 4.24, 4.51); ^{1}H-NMR δ(200 MHz, pyridine-d_5) 1.7-2.0 (3H, m) and 2.5-3.0 (3H, m), 3.7 (1H, m, H-3), 7.3-7.5 (2H, m, H-8,9), 7.8 (1H, m, H-7 or 10), 7.95 (1H, m, H-10 or 7). Found: C 64.92; H 5.34; N 23.34. Calc. for $C_{13}H_{12}N_4O$: C 64.98; H 5.03; N 23.32%.

2-Methyl, 10(1'-methyl-2'-ethoxycarbonyl-vinyl)amino pyrimido[1,2-a]benzimidazol-4-one (5a) Crystals from methanol (7%); mp 168-171°C; IR(KBr): 3270 (N-H), 1700 (C=O, CO_2Et), 1670 (C_4=O), 1615 and 1600 (C=N, C=C) cm^{-1}. UV λ_{max} MeOH (log ε) 329, 258, 215 nm (4.18, 4.26, 4.52); ^{1}H-NMR δ(200 MHz, $CDCl_3$) 1.31 (3H, t, CH_3-CH_2O), 1.75 (3H, s, Me-1'), 2.39 (3H, s, Me-2), 4.20 (2H, q, OCH_2-CH_3), 5.01 (1H, s, H-2'), 6.10 (1H, s, H-3), 7.43 (3H, m, H-7,8,9), 8.64 (1H, m, H-6), 10.38 (1H, s, NH). Found: C 62.55; H 5.80; N 17.40. Calc. for $C_{17}H_{18}N_4O_3$: C 62.56; H 5.56; N 17.17%.

2,7,8-Trimethyl-10(1'-methyl-2'-ethoxycarbonyl-vinyl)amino pyrimido[1,2-a]benzimidazol-4-one (5b) Crystals from ethanol (10%); mp 188-191°C; IR(KBr): 3270 (N-H), 1700 (C=O, CO_2Et), 1670 (C_4=O), 1615 and 1600 (C=N, C=C) cm^{-1}. UV λ_{max} MeOH (log ε) 328, 258, 219 nm (4.28, 4.44, 4.68); ^{1}H-NMR δ(60 MHz, DMSO-d_6) 1.25 (3H, t, CH_3-CH_2-O), 2.2-2.3 (12H, overlapped, s, Me-2,7,8,1'), 4.15 (2H, q, OCH_2-CH_3), 4.9 (1H, s, H-2'), 6.0 (1H, s, H-3), 7.1 (1H, s, H-9), 8.2 (1H, s, H-6) 10.25 (1H, ws, NH). Found: C 64.50; H 6.25; N 15.70. Calc. for $C_{19}H_{22}N_4O_3$: C 64.38; H 6.25; N 15.81%.

2,3-Tetramethylene-10(2'-ethoxycarbonylcyclohexenyl)amino pyrimido[1,2-a]benzimidazol-4-one (8) Crystals from ethanol (4%); mp 197-199°C; IR(KBr): 3270 (N-H), 1680 (CO_2Et), 1655 (C=O), 1615 and 1600 (C=N, C=C) cm^{-1}. UV λ_{max} MeOH (log ε) 327, 260, 227, 214 nm (4.24, 4.35, 4.57, 4.54); ^{1}H-NMR δ(200 MHz, $CDCl_3$) 1.33 (3H, t, CH_3-CH_2O), 1.59 (6H, m), 1.82 (6H, m), 2.64-2.78 (4H, m), 4.23 (2H, m, OCH_2-CH_3), 7.35 (3H, m, H-7,8,9), 8.63 (1H, m, H-6), 10.65 (1H, s, NH). Found: C 68.10; H 6.50; N 14.00. Calc. for $C_{23}H_{26}N_4O_3$: C 67.95; H 6.44; N 13.78%.

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