# CONDENSED IMIDAZO-1,2,4-TRIAZINES.

# 23.* SYNTHESIS AND REACTIONS OF 2-(1'-ALKYLHYDRAZINO)-BENZIMIDAZOLE WITH ACETYL(BENZOYL)ACETONE

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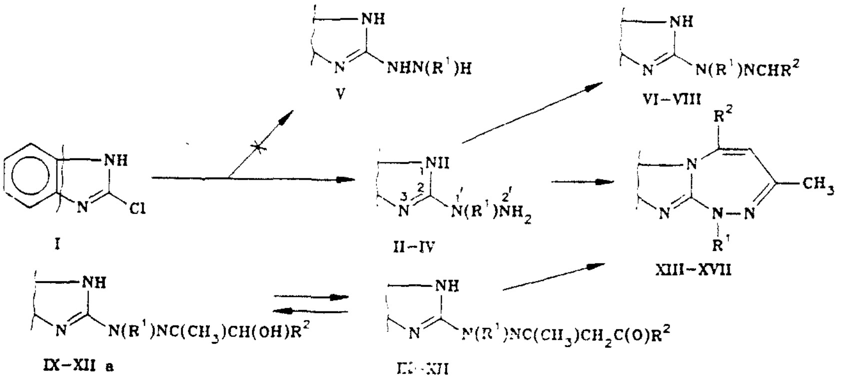
*By reaction of 2-chlorobenzimidazole with methyl-, ethyl-, and 2-hydroxyethylhydrazine we have synthesized the corresponding 2-(1'-alkylhydrazino)benzimidazoles for the first time. By refluxing the latter in alcohols with acetyl(benzoyl)acetone they form 1-(2-benzimidazolyl)-1-alkylhydrazones and, without solvent, form 1,3,5-trisubstituted 1,2,4-triazepino[4,3-*a*]benzimidazoles.*

We were unable to obtain 1,2,4-triazepino[4,3-*a*]benzimidazoles by reaction of 2-hydrazinobenzimidazole with acetylacetone. As shown by calculation,[†] the reason for this is the higher electron density on the hydrazine nitrogen atom than on the $N_1$ ring atom. Consequently, nucleophilic attack of acetyl acetone on the hydrazine fragment of the benzimidazole leads to formation of 2-(3,5-dimethylpyrazol-1-yl)benzimidazole [2]. Prevention of such cyclization is possible by incorporation of a substituent at $N_{1'}$. We have studied the reaction of 2-chlorobenzimidazole (I) with methyl-, ethyl-, and 2-hydroxyethylhydrazine in order to synthesize the 2-(1'-alkylhydrazino)benzimidazoles II-IV. By changing the solvent and the ratio of starting materials we have found that the optimal procedure for synthesis of II and IV involves refluxing benzimidazole I with a tenfold (molar) excess of 50% methyl(β-hydroxyethyl)hydrazine. For the ethyl derivative III the best yield was achieved when the reaction was carried out in anhydrous ethylhydrazine.



II, VI, VII, IX, X, XVII $R^1=CH_3$; III, VIII, XI—XIV $R^1=C_2H_5$; IV, XV, XVI $R^1=(CH_2)_2OH$; VI, X, XII, XIV, XVI $R^2=C_6H_5$; VII, VIII $R^2=4\text{-}NO_2C_6H_4$; IX, XI, XIII, XV, XVII $R^2=CH_3$

When refluxed in ethanol with aromatic aldehydes the 2-alkylhydrazinobenzimidazoles II, III yield the hydrazones VI-VIII in high yields, thus showing the presence of amino groups in the hydrazine part of the molecule. The structure of the hydrazine VI was also confirmed spectroscopically (Tables 1 and 2).

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*For Communication 22, see [1].

[†] According to calculation carried out by [3], the charges of atoms $N_1$, $N_{1'}$, and $N_{2'}$ are +0.281, +0.163, and +0.016, respectively.

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TABLE 1. PMR Spectra of Compounds Synthesized

| Compound | Chemical shift, δ, ppm |
|---|---|
| II | 3,34 (3H, s, $CH_3$); 4,78 (2H, s, $NH_2$); 6,91 . . . 7,37 (4H, m, Ar); 11,06 (1H, s, NH) |
| III | 1,17 (3H, t, $CH_2CH_3$, $J=30$ Hz); 3,68 (2H, q, $CH_2CH_3$, $J=30$ Hz); 4,84 (2H, s, $NH_2$); 6,90 . . . 7,50 (4H, m, Ar); 11,15 (1H, s, NH) |
| VI | 3,56 (3H, s $CH_3$); 6,90 . . . 8,01 (10H, m, Ar, $=CH$); 11,70 (1H, s NH) |
| IX | 1,92 (3H, s $CH_3—C=O$); 1,99 (3H, s $CH_3—C=O$); 2,25 (3H, s, $CH_3—C=N$); 2,52 (2H, s, $CH_2$); 3,22 (3H, s, $CH_3N$); 3,24 (3H, s, $CH_3N$); 5,21 (1H, s $HC=C—$); 6,91 . . . 7,32 (4H, m, Ar); 8,95 (1H, s OH); 11,33 (1H, s, NH); 11,56 (1H, s, NH) |
| XI | 1,33 (3H, s, $CH_3CH_2$, $J=9$ Hz); 1,96 (3H, s $CH_3—C=$); 2,13 (3H, s, $CH_3—C=O$); 2,11 (2H, q, $CH_2—CH_3$, $J=9$ Hz); 2,58 (2H, s, $—CH_2—$); 7,10 . . . 7,36 (4H, m, Ar); 10,35 (1H, s, NH) |
| XIV | 1,34 (3H, t, $CH_3CH_2$, $J=9$ Hz); 2,66 (3H, s, $CH_3—C=$); 3,98 (2H, q, $CH_2—CH_3$, $J=9$ Hz); 7,29 . . . 7,60 (10H, m, Ar, $=CH$) |

TABLE 2. Mass Spectra of II-IV, VI, IX-XIV

| Compound | m/z (I, % of maximum)* |
|---|---|
| II | 65 (26), 69 (28), 91 (21), 92 (46), 118 (61), 119 (38), 133 (20), 146 (51), 147 (67), 161 (19), 162 (100) |
| III | 65 (55), 90 (26), 91 (41), 92 (84), 118 (31), 119 (36), 133 (26), 147 (100), 148 (35), 160 (28), 176 (93) |
| IV | 65 (47), 90 (39), 91 (45), 92 (63), 118 (100), 119 (40), 132 (40), 146 (96), 147 (74), 148 (94), 192 (78) |
| VI | 51 (56), 77 (23), 78 (43), 88 (34), 92 (20), 118 (64), 119 (44), 146 (100), 147 (89), 148 (10), 173 (19,9), 250 (54) |
| IX | 43 (56), 51 (58), 65 (12), 92 (18), 118 (58), 119 (38), 146 (100), 145 (46), 187 (84), 188 (12), 201 (11), 244 (41) |
| X | 77 (40), 92 (20), 103 (25), 104 (22), 105 (44), 118 (57), 119 (45), 146 (100), 147 (42), 187 (97), 306 (19) |
| XI | 43 (47), 67 (15), 93 (16), 105 (14), 119 (19), 133 (12), 146 (10), 160 (100), 161 (10), 201 (17), 258 (8) |
| XII | 77 (68), 90 (23), 105 (73), 118 (31), 119 (24), 133 (21), 146 (46), 160 (100), 161 (29), 201 (96), 320 (18) |
| XIII | 63 (17), 65 (21), 92 (19), 156 (29), 157 (42), 183 (25), 211 (13), 212 (83), 225 (75), 239 (14), 240 (100) |
| XIV | 43 (13), 65 (18), 77 (18), 92 (19), 218 (13), 219 (19), 243 (16), 273 (43), 287 (44), 301 (100), 302 (98) |

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*$M^+$ and 10 most abundant ions are given.

TABLE 3. Physical Data for Synthesized Compounds

| Compound | Empirical formula | mp, °C | Yield, % |
|---|---|---|---|
| II | $C_8H_{10}N_4$ | 237 . . . 241 | 96 |
| III | $C_9H_{12}N_4$ | 183 . . . 186 | 70 |
| IV | $C_9H_{12}N_4O$ | 164 . . . 165 | 30 |
| VI | $C_{12}H_{14}N_4$ | 262 . . . 264 | 93 |
| VII | $C_{15}H_{13}N_5O_2$ | 266 . . . 267 | 96 |
| VIII | $C_{16}H_{15}N_5O_2$ | 274 . . . 276 | 97 |
| IX | $C_{13}H_{16}N_4O$ | 204 . . . 206 | 67 |
| X | $C_{16}H_{18}N_4$ | 208 . . . 210 | 97 |
| XI | $C_{14}H_{18}N_4O$ | 180 . . . 181 | 80 |
| XII | $C_{19}H_{20}N_4O$ | 174 . . . 175 | 41 |
| XIII | $C_{14}H_{16}N_4$ | 230 . . . 231 | 54 |
| XIV | $C_{19}H_{20}N_4$ | 185 . . . 187 | 68 |
| XV | $C_{14}H_{16}N_4O$ | 255 . . . 257 | 52 |
| XVI | $C_{19}H_{18}N_4O$ | 240 . . . 241 | 49 |
| XVII | $C_{13}H_{14}N_4$ | 260 . . . 262 | 45 |

Refluxing hydrazines II, III with acetyl-, or benzoylacetone in methanol, ethanol, or isopropanol gives the 1-(2-benzimidazolyl)-1-alkylhydrazones IX-XII.

The PMR spectra of the hydrazones IX, XI (Table 1) confirm their structure. The PMR spectrum of IX shows the presence of a hydroxyl proton at 8.95 ppm, a methyl group on a double bond (1.95 ppm), and a methine proton at 5.21 ppm which point to the enol form IXa for the product. This conclusion agrees with the mass spectral data for hydrazone IX in which there are observed $[M - COCH_3]^+$ and $[M - OH]^+$ ion peaks (the enol content being ~30% according to the mass spectrum [4]). Parallel fragmentations of the molecular ions by fission of the side chain are not dependent upon the tautomeric form and so identify the structure of the hydrazone part of the molecule.

In the case of X-XII, mass spectral data show exclusively the keto forms with $C_6H_5CO^+$ and $[M - C_6H_5CO]^+$ ions for X, XII and $CH_3CO^+$ for XI. General fragmentation pathways for IX-XII are processes involving fission of the N–N bond in the hydrazine part of the molecule (Table 2).

When refluxed in DMF the hydrazones IX, XI, XII cyclize to form the corresponding tri-substituted 1,2,4-triazepino[4,3-*a*]benzimidazoles XIII, XIV, XVII (Table 3). Compounds XIII-XVI are also formed by heating the hydrazinobenzimidazoles III, IV with acetyl(benzoyl)acetone at 150-160°C without solvent.

In contrast to the hydrazones (XI, XII), the mass spectral fragmentation of the triazepine tricycles XIII, XIV does not occur at the N–N bond. The first stage of the decomposition of $M^+$ is elimination of $H^{\cdot}$, $CH_3^{\cdot}$ (immonium ion) and $C_2H_5^{\cdot}$ which is characteristic of N-alkyl substituted heterocycles [5]. There then follows elimination of $N_2$ or $CH_3CN_2$ from the ion $[M - C_2H_5]^+$ which shows the presence of the aza fragment in the seven-membered heterocycle and defines the location of the atoms within it. Accurate mass measurement for the $[M - C_2H_5, -CH_3CN_2]^+$ ion in XIV (found: 218.0847; calculated: 218.0844 for $C_{15}H_{10}N_2$) and PMR spectral data confirm the proposed structure.

## EXPERIMENTAL

Proton magnetic resonance spectra were obtained on a Bruker WH-90 instrument ($CDCl_3$ solvent) using TMS internal standard. Mass spectra were recorded on a Varian MAT-311A (direct introduction into the ion source, ionization energy 70 eV). High-resolution mass spectra were taken under the same conditions. Compounds II, III were used without additional purification and those remaining were recrystallized from water (IV, XV), aqueous acetic acid (VI), glacial acetic acid (VII, VIII), aqueous methanol (IX, X, XI, XIII), ethyl acetate (XII, XIV), or methanol (XVI, XVIII).

Elemental analytical data (C, H, N) for II-IV, VI-XVII agreed with those calculated.

**2-(1'-Alkylhydrazino)benzimidazoles (II-IV).** A suspension of 2-chlorobenzimidazole (2 g, 13 mmoles) and methyl- or β-hydroxyethylhydrazine (50%, 130 mmoles) was refluxed for 2 h. After cooling the precipitate of II, IV evolved was filtered off and washed with cold water.

**Compound III** was obtained by refluxing 2-chlorobenzimidazole (1.2 g, 7 mmoles) and ethylhydrazine (4.7 g, 70 mmoles) for 2 h.

**Arylaldehyde 1-(2-Benzimidazolyl)-1-alkylhydrazones (VI-VIII).** The arylaldehyde (5 mmoles) was added to a solution of the hydrazine II, III (5 mmoles) in ethanol (5 ml), and refluxed for 1 h. The precipitated solid was filtered off and washed successively with methanol and ether.

**Acetyl(benzoyl)acetone 1-(2-Benzimidazolyl)-1-alkylhydrazones (IX-XII).** A solution of the hydrazine II, III (5 mmoles) and acetyl(benzoyl)acetone (5 mmoles) in ethanol was refluxed for 2 h. The solid precipitated on cooling was filtered off and washed with ether.

**1,3,5-Tri-substituted 1,2,4-Triazepino[4,3-*a*]benzimidazole (XIII-XVII).** **A.** A mixture of hydrazine III, IV (5 mmoles) and acetyl(benzoyl)acetone (8 mmoles) was heated in a 150-160°C bath for 2 h. The mixture was cooled, diluted with ether (5 ml), and the precipitated solid filtered off and washed with ether.

**B.** Hydrazones IX, XI, XII (5 mmoles) were refluxed in DMF (4 ml) for 3 h. After cooling, water (1 ml) was added and the precipitate filtered off and washed with water to give XIII, XIV, XVII in 78, 76, and 48% yields, respectively.

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