Heterocyclic Rearrangements. Phenylhydrazones and *N*-Methyl-*N*-phenylhydrazones of 3-Acylisoxazoles [1]

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The reaction of 3-benzoyl-5-phenylisoxazole (**4**) and 3-acetyl-5-methylisoxazole (**5**) with phenylhydrazine and *N*-methyl-*N*-phenylhydrazine has been investigated and the reactivity of *(E)*- and *(Z)*-phenylhydrazones and *N*-methyl-*N*-phenylhydrazones has been studied.

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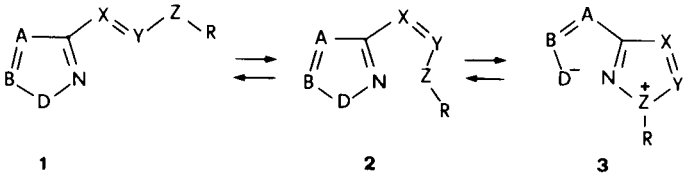
In the framework of our researches concerning heterocyclic rearrangements, recently [2] we paid attention to the system **1** ⇋ **2** ⇋ **3**. In this connection, studying the behaviour of *(E)*- and *(Z)*-phenylhydrazones [3] and *N*-methyl-*N*-phenylhydrazones [2] of 3-benzoyl-5-phenyl-1,2,4-oxadiazole, we showed a marked reactivity of the *(Z)*-*N*-methyl-*N*-phenylhydrazone (unisolated) in the reaction involving attack on the ring nitrogen atom by the methyl phenyl substituted nitrogen. Continuing our researches on this aspect of heterocyclic rearrangements, we now have investigated the behaviour of *(E)*- and *(Z)*-phenylhydrazones and *N*-methyl-*N*-phenylhydrazones of 3-acylisoxazoles **4** and **5**.

Scheme 1

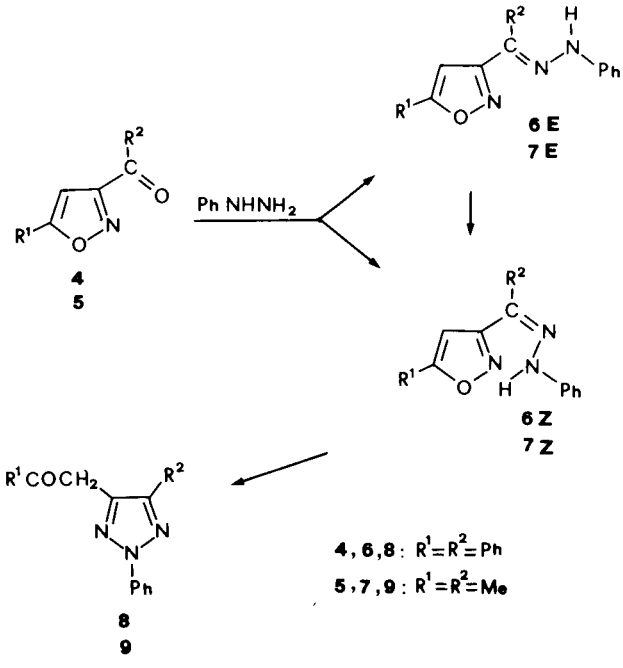


1 **2** **3**

In the case of the reaction between 3-benzoyl-5-phenylisoxazole (**4**) and phenylhydrazine, only the synthesis of the *Z*-isomer phenylhydrazone **6Z** has been reported [4]. However, performing the reaction in acetic acid as solvent at room temperature, we isolated both **6Z** and **6E** in 55% and 26% yield, respectively. When both isomers were dissolved in acetic acid an *E* ⇋ *Z* equilibrium was observed, without formation of the rearrangement product **8**. The rearrangement of **6Z** and **6E** into **8** took place by the action of sodium ethoxide in ethanol, and in this instance **6E** showed a slower process involving a prior **6E** to **6Z** isomerization [5].

Also in the reaction between **4** and *N*-methyl-*N*-phenylhydrazine in acetic acid we observed the formation of both **10Z** and **10E**. However, it was difficult to isolate **10Z** directly from the reaction mixture. In fact, while at the initial stage of the reaction, besides the starting ketone **4**, both isomers were present. In the course of the reaction **10Z** rearranged into the triazole **8** through demethylation [2] of **12**. In turn, the formed **8** partially reacted with *N*-methyl-*N*-phenylhydrazine giving the indole **16** through a Fischer indolization of **14** (unisolated). At the end of the reaction (*ca.* 50 hours), a suitable procedure allowed us to isolate **10E**, **8**, and **16**. A support to the formation of **16** was provided by the observation that compound **8** reacted with *N*-methyl-*N*-phenylhydrazine in acetic acid at room temperature giving the indole **16**. When dissolved in acetic acid, **10E** gave a mixture of both isomers from which we obtained a pure sample of **10Z**. Under this treatment a slow rearrangement into **8** also took place. A faster isomerization/rearrangement of **10E** into **8** was achieved by refluxing it in acetic acid or in ethanol in the presence of hydrochloric acid, where the chloride anion would act as a demethylating agent [6] on **12**.

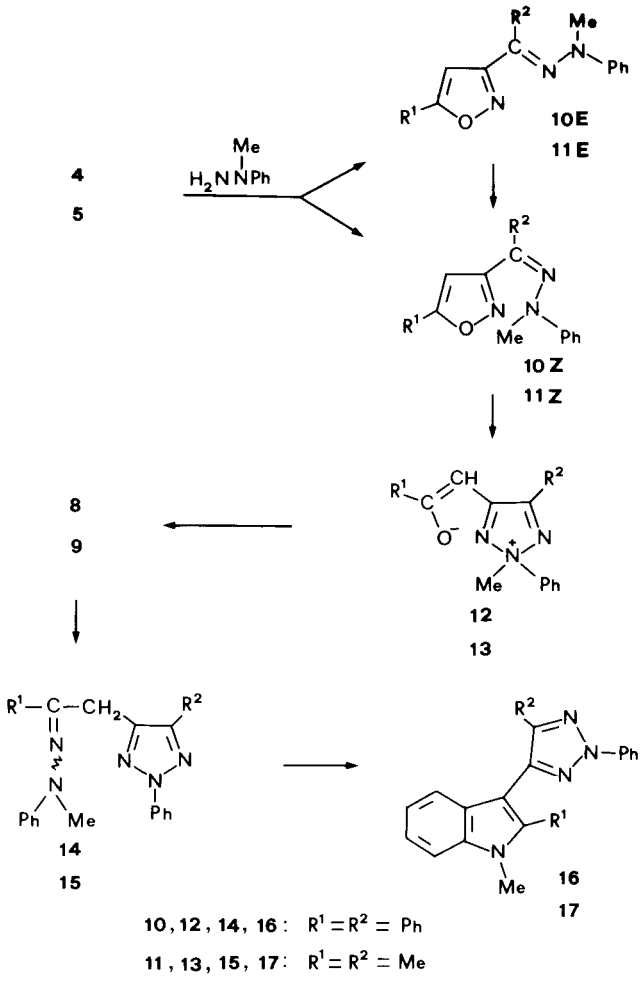
Scheme 2



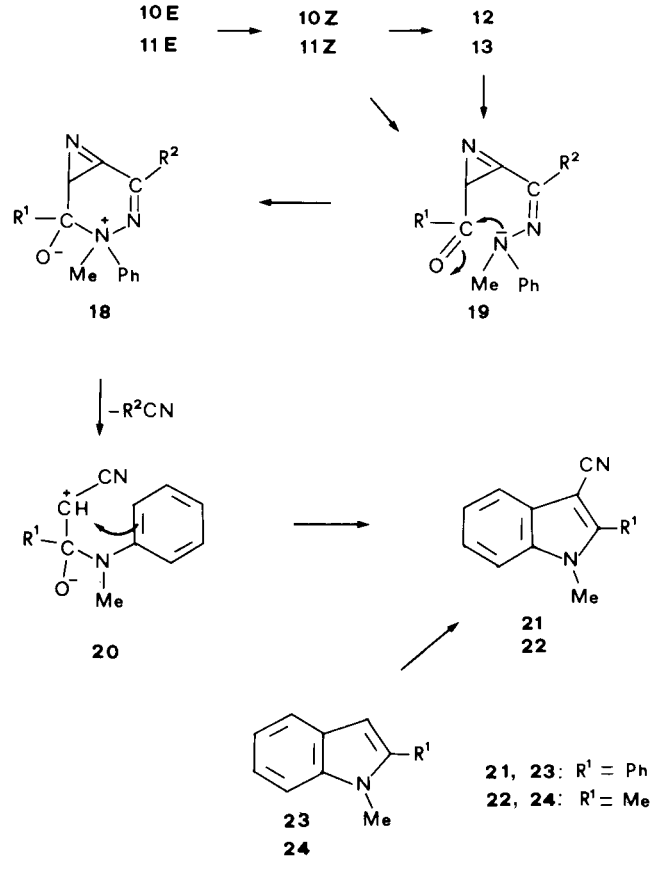
4 **5** **6E** **7E** **6Z** **7Z** **8** **9**

Different products were obtained from the hydrazone **10E** in the absence of a demethylating agent. When refluxed in ethanol, while compound **6E** remained unchanged, the *(E)*-*N*-methyl-*N*-phenylhydrazone **10E** gave benzonitrile and 1-methyl-2-phenyl-3-cyanoindole (**21**) [7], whose structure was confirmed through a comparison with a sam-

Scheme 3



Scheme 4



ple prepared by cyanation of 1-methyl-2-phenylindole (**23**) with chlorosulphonylisocyanate [8]. Starting from **10Z** a faster rearrangement was observed. Although we have no evidences for the nature of the intermediates involved, tentatively the formation of the indole **21** could be explained in terms of Scheme 4, involving *a priori* *E* to *Z* isomerization and, probably, an azirine intermediate **19** [9].

In the case of the reaction between 3-acetyl-5-methylisoxazole (**5**) and phenylhydrazine, only the synthesis of the *E*-isomer phenylhydrazone **7E** has been reported [10]. However, performing the reaction in ethanol, we isolated **7E** and **7Z** (14%) as well. When dissolved in acetic acid both isomers gave a fast $E \leftrightharpoons Z$ equilibrium, where trace amounts of **7Z** were present, without formation of the triazole **9**. As for the thermally-induced rearrangement, reported [10] only for the available *E*-isomer **7E**, we observed that both isomers gave the process **7E** $\leftrightharpoons$ **7Z** $\rightarrow$ **9**. Moreover, we found that, when treated with sodium ethoxide in ethanol, only **7Z** smoothly rearranged into **9**.

In the case of the reaction between **5** and *N*-methyl-*N*-phenylhydrazine in acetic acid or in ethanol, we were able to isolate only the *E*-isomer **11E**. This latter, when refluxed in acetic acid gave the foreseen pathway, *i.e.*, i) isomerization of **11E** to **11Z** (undetected); ii) rearrangement and demethylation to **9**. When refluxed in ethanol the *(E)*-*N*-methyl-*N*-phenylhydrazone **11E** remained unchanged, thus differing from the corresponding **10E** of the 3-benzoyl series. However, by refluxing in ethanol in the presence of catalytic amounts of acetic acid, compound **11E** gave the 1,2-dimethyl-3-cyanoindole (**22**) [11] directly (see Scheme 4), or a mixture of **9** and **22** when more amounts of acetic acid were used. Rearrangement of **11E** into **22** also took place by carefully melting it at 120°.

As previously observed [2], phenylhydrazones and *N*-methyl-*N*-phenylhydrazones behave differently in isomerization as well as in rearrangement. The *(Z)*-*N*-methyl-*N*-phenylhydrazone sequence exhibits a marked reactivity in rearrangement; the isolation of the *(Z)*-*N*-methyl-*N*-phenylhydrazone **10Z** can be due to the lower tendency to rearrangement of the isoxazole ring with respect to the 1,2,4-oxadiazole [12]. The different behaviour between 3-benzoyl- and 3-acetylisoxazole derivatives can be due to the geometric features in the phenylhydrazone moiety.

EXPERIMENTAL

Melting points were determined with a Kofler hot-stage apparatus. The ir spectra (nujol, unless otherwise specified) were determined with Perkin Elmer 257 instrument, uv spectra (methanol) with a Zeiss PMQ II spectrophotometer, ^{1}H nmr spectra (60 MHz) with a Varian EM 360 spectrometer (tetramethylsilane as the internal standard), and mass spectra with a JEOL JMS 01-SG-2 instrument (75 eV). Dry column chromatography was performed on Riedel silica gel (0.063-0.2 mm) deactivated with water (15%). Light petroleum refers to that fraction boiling in the range 40-60°.

3-Benzoyl-5-phenylisoxazole (**4**) [5b] and 3-acetyl-5-methylisoxazole (**5**) [13] were prepared as reported. Configuration of phenylhydrazones and *N*-methyl-*N*-phenylhydrazones has been assigned on the basis of spectroscopic evidences (uv, ir, nmr).

Reaction of 3-Benzoyl-5-phenylisoxazole (**4**) with Phenylhydrazine.

To a solution of compound **4** (2 g) in acetic acid (30 ml), phenylhydrazine (1.2 ml) was added, and the mixture was kept at room temperature. After 48 hours the yellow product was filtered off giving the *(Z)*-phenylhydrazone **6Z** (0.5 g), mp 108° (from ethanol), lit [5] mp 105-108°; uv λ max (log ε) 275 nm (4.35) and 360 nm (4.32); ir: 3220 cm^{-1} (NH); ir (chloroform): 3230 cm^{-1} (NH); nmr (deuteriochloroform): δ 6.54 (s, CH, 1H), 6.9-7.9 (m, aromatic, 15H), 11.0 (s, NH, 1H).

Dilution of the mother liquor with water and filtration gave a mixture of both isomers which was chromatographed with cyclohexane-ethyl acetate (30:1), giving at first additional amounts of **6Z** (1 g, total yield 55%), and then the *(E)*-phenylhydrazone **6E** (0.7 g, 26%), mp 120° (from benzene-light petroleum); uv: λ max (log ε) 255 nm (4.37) and 330 nm (4.21); ir (nujol, chloroform): 3320 cm^{-1} (NH); nmr (deuteriochloroform): δ 6.9-8.0 (m, CH, NH, and aromatic, 17H); nmr (DMSO-d_6): δ 7.1-8.1 (m, CH, aromatic, 16H), 9.55 (s, NH, 1H).

Anal. Calcd. for $C_{22}H_{17}N_3O$: C, 77.85; H, 5.05; N, 12.38. Found: C, 77.9; H, 5.15; N, 12.4.

Rearrangement of *(E)*- and *(Z)*-Phenylhydrazones **6E** and **6Z**.

A solution of compound **6Z** (0.15 g) in ethanol (20 ml) containing sodium ethoxides (from 0.05 g of sodium) was refluxed for 15 minutes. After removal of the solvent, water was added to the residue. Extraction with ether and evaporation gave a residue which was chromatographed with cyclohexane-ethyl acetate (20:1) giving 2,4-diphenyl-5-phenacyl-1,2,3-triazole (**8**) (0.1 g, 67%), mp 87° (from light petroleum), lit [5b] as an oil; ir 1680 cm^{-1} (C=O); nmr (deuteriochloroform): δ 4.6 (s, CH_2, 2H), 7.2-8.2 (m, aromatic, 15H).

Compound **6E** under identical conditions gave **8** after refluxing 5 hours.

Reaction of 3-Benzoyl-5-phenylisoxazole (**4**) with *N*-Methyl-*N*-phenylhydrazine.

To a solution of compound **4** (3 g) in acetic acid (35 ml), *N*-methyl-*N*-phenylhydrazine (1.8 ml) was added and the mixture was kept at room temperature. After 50 hours, when tlc indicated the absence of the starting ketone, the solid was filtered off and washed with the minimum of acetic acid. The solid was dissolved in ether which was washed with aqueous sodium hydrogen carbonate and then evaporated affording the *(E)*-*N*-methyl-*N*-phenylhydrazone **10E** (1.8 g), mp 120° (from light petroleum); uv: λ max (log ε) 252 nm (4.47) and 340 nm (4.06); nmr (deuteriochloroform): δ 3.0 (s, N—Me, 3H), 7.15 (s, CH, 1H), 7.2-8.0 (m, aromatic, 15H).

Anal. Calcd. for $C_{23}H_{19}N_3O$: C, 78.16; H, 5.42; N, 11.89. Found: C, 78.2; H, 5.5; N, 11.9.

The mother liquor was diluted with water and extracted with ether. The ethereal extracts were washed with sodium hydrogen carbonate, dried, evaporated, and the residue was chromatographed with cyclohexane-ethyl acetate (99:1). First fractions gave a residue which was taken up with light petroleum yielding the indole **16**, (0.3 g, 6%), mp 175° (from ethanol); nmr (deuteriochloroform): δ 3.7 (s, N—Me, 3H), 7.1-8.4 (m, aromatic, 19H); ms: m/z 426 (M$^+$).

Anal. Calcd. for $C_{29}H_{22}N_4$: C, 81.66; H, 5.2; N, 13.14. Found: C, 81.5; H, 5.1; N, 13.2.

Subsequent elution gave additional amounts of the *(E)*-*N*-methyl-*N*-phenylhydrazone **10E** (0.7 g, total yield 2.5 g, 60%), and then compound **8** (0.3 g, 8%).

To a solution of compound **8** (0.3 g) in acetic acid (10 ml) *N*-methyl-*N*-phenylhydrazine (0.15 ml) was added and the mixture was kept at room temperature. After 48 hours, filtration of the product separated giving 1-methyl-2-phenyl-3-(2,5-diphenyl-1,2,3-triazol-4-yl)indole (**16**) (0.3 g, 80%), mp 175° (from ethanol) (see above).

Isomerization and Rearrangement of **10E** in Acetic Acid.

A solution of **10E** (1 g) in acetic acid (75 ml) was kept at room temperature. After 24 hours water was added and the crude mixture was filtered off and chromatographed with light petroleum-ethyl acetate (99:1). At first one obtained the *(Z)*-*N*-methyl-*N*-phenylhydrazone **10Z** (0.15 g, 15%), mp 98° (from light petroleum); uv: λ max (log ε) 256 nm (4.49), and 350 nm (4.0); nmr (deuteriochloroform): δ 3.25 (s, N—Me, 3H), 6.7 (s, CH, 1H), 6.9-8.1 (m, aromatic, 15H).

Anal. Calcd. for $C_{23}H_{19}N_3O$: C, 78.16; H, 5.42; N, 11.89. Found: C, 78.2; H, 5.4; N, 12.0.

Subsequent elution gave **10E** (0.5 g, 50%), and then small amounts of the triazole **8**.

On refluxing (20 minutes) in acetic acid (15 ml), after working as usual, compound **10E** (0.5 g) gave **8** (0.35 g, 70%). On refluxing (2 hours) in ethanol (20 ml) containing concentrated hydrochloric acid (0.1 ml), compound **10E** (0.3 g) also gave **8** (0.2 g, 67%).

Rearrangement of *(E)*-*N*-Methyl-*N*-phenylhydrazone **10E** in Ethanol.

A solution of *(E)*-*N*-methyl-*N*-phenylhydrazone **10E** (1 g) in ethanol (40 ml) was refluxed for 15 hours. Tlc analysis showed the intermediate formation of **10Z**, and glc analysis revealed the presence of benzonitrile. Evaporation of the solvent and chromatography of the residue with cyclohexane-ethyl acetate (5:1) gave 1-methyl-2-phenyl-3-cyanoindole (**21**) (0.5 g, 80%), mp 116-118° (from ethanol), lit [7] mp 117-119°; ir: 2220 cm^{-1} (CN); nmr (DMSO-d_6): δ 3.75 (s, N—Me, 3H), 7.2-7.8 (m, aromatic, 9H).

A sample of **21** was prepared by cyanation of 1-methyl-2-phenylindole (**23**) with chlorosulphonylisocyanate in dimethylformamide-acetonitrile according to the procedure reported [8].

Reaction of 3-Acetyl-5-methylisoxazole (**5**) with Phenylhydrazine.

To a solution of compound **5** (3 g) in ethanol (15 ml), phenylhydrazine (3.2 ml) was added, and the mixture was kept at room temperature. After 2 hours the solid was filtered off and washed with ethanol affording the *(E)*-phenylhydrazone **7E** (3.4 g), mp 169° (from ethanol), lit [10] mp 165° ; ir: 3280 cm^{-1} (NH); ir (chloroform): 3360 cm^{-1} (NH); nmr (deuteriochloroform): δ 2.28 and 2.43 (2 singlets, 2 × Me, 6H), 6.45 (s, CH, 1H), 6.9-7.6 (m, aromatic and NH, 6H); nmr (DMSO-d_6): δ 9.75 (s, NH, 1H); uv: λ max (log ε) 320 nm (4.36).

Evaporation of the mother liquor gave a residue which was chromatographed by using cyclohexane-ethyl acetate 30:1 as eluent, giving the *(Z)*-phenylhydrazone **7Z** (0.9 g, 14%), mp 77° (from light petroleum); ir: 3260 cm^{-1} (NH); ir (chloroform): 3250 cm^{-1} (NH); nmr (deuteriochloroform): δ 2.28 and 2.43 (2 singlets, 2 × Me, 6H), 6.01 (s, CH, 1H), 6.9-7.3 (m, aromatic, 5H), 10.9 (s, NH, 1H); uv: λ max (log ε) 335 nm (4.26).

Anal. Calcd. for $C_{12}H_{13}N_3O$: C, 66.95; H, 6.09; N, 19.52. Found: C, 67.0; H, 6.0; N, 19.5.

Subsequent elution gave additional amounts of **7E** (0.2 g, total yield 56%).

Rearrangement of *(E)*- and *(Z)*-Phenylhydrazones **7E** and **7Z**.

Heating each of both isomers at 180° (3 hours) gave 4-acetonyl-5-methyl-2-phenyl-1,2,3-triazole (**9**) (60%), mp 85° (from light petroleum), lit [10] mp 85°; ir: 1710 cm^{-1} (C=O); nmr (deuteriochloroform): δ 2.20 and 2.30 (2 singlets, 2 × Me, 6H), 3.90 (s, CH_2, 2H), 7.2-8.1 (m, aromatic, 5H).

A solution of compound **7Z** (0.2 g) in ethanol (15 ml) containing

sodium ethoxide (from 0.05 g of sodium) was refluxed for two minutes. Working up as usual, after chromatographic purification with light petroleum-ethyl acetate (20:1), gave the triazole **9** (50%).

Refluxing (2 hours) compound **7E** in identical conditions left it unchanged.

Reaction of 3-Acetyl-5-methylisoxazole (**5**) with *N*-Methyl-*N*-phenylhydrazine.

To a solution of compound **5** (3 g) in acetic acid (15 ml) *N*-methyl-*N*-phenylhydrazine (3.5 ml) was added. After 1 hour at room temperature water was added and the mixture was extracted with ether. The ethereal extracts were washed to remove acetic acid, dried and evaporated. Chromatography of the residue with cyclohexane-ethyl acetate (30:1) gave the *(E)*-*N*-methyl-*N*-phenylhydrazone **11E** (4.5 g, 82%) as a yellow oil which solidified on freezing; nmr (deuteriochloroform): δ 2.3 and 2.4 (2 singlets, 2 × C—Me, 6H), 3.25 (s, N—Me, 3H), 6.5 (s, CH, 1H), 6.9-7.4 (m, aromatic, 5H).

Anal. Calcd. for $C_{13}H_{15}N_3O$: C, 68.1; H, 6.59; N, 18.33. Found: C, 68.2; H, 6.5; N, 18.4.

Behaviour of the *(E)*-*N*-Methyl-*N*-phenylhydrazone **11E**.

a) In Acetic Acid.

A solution of compound **11E** (0.8 g) in acetic acid (10 ml) was refluxed for 1 hour. Dilution with water, extraction with ether, working up as usual and chromatography with cyclohexane-ethyl acetate (10:1) gave at first 1,2-dimethyl-3-(2-phenyl-5-methyl-1,2,3-triazol-4-yl)indole (**17**) (0.1 g), mp 116° (from light petroleum); nmr (deuteriochloroform): δ 2.40 and 2.45 (2 singlets, 2 × C—Me, 6H), 3.75 (s, N—Me, 3H), 7.10-8.30 (m, aromatic, 9H); ms: m/z 302 (M^+).

Anal. Calcd. for $C_{19}H_{18}N_4$: C, 75.47; H, 6.0; N, 18.53. Found: C, 75.5; H, 6.1; N, 18.6.

Subsequent elution gave the triazole **9** (0.4 g, 53%).

The formation of the indole **17** can be explained as for **16**, considering that partial hydrolysis of starting material **11E** could furnish *N*-methyl-*N*-phenylhydrazine which, in turn, reacted with the formed **9**. In fact, on refluxing (1 hour) compound **9** (0.4 g) in acetic acid (10 ml) with *N*-methyl-*N*-phenylhydrazine (0.3 ml), after working up as usual and chromatographic purification gave the indole **17** (0.3 g, 53%).

b) In Ethanol.

On refluxing (5 hours) in ethanol, compound **11E** remained unchanged. On refluxing (5 hours) a solution of compound **11E** (0.3 g) in ethanol (30 ml) containing acetic acid (0.1 ml), after wroking up as usual gave small amounts of compound **9** and then 1,2-dimethyl-3-cyanoindole (**22**) (0.15 g, 68%), mp 106° (from light petroleum), lit [11] mp 104-105°; ir: 2215 cm^{-1} (CN); nmr (DMSO-d_6): δ 2.55 (s, C—Me, 3H), 3.75 (s, N—Me, 3H), 7.2-7.8 (m, aromatic, 4H).

A sample of **22** has been obtained as for **21** according to the procedure reported in [8].

On refluxing (5 hours) in ethanol (30 ml) containing acetic acid (0.5 ml), compound **11E** (0.3 g) gave **9** (0.1 g, 36%) and **22** (0.05 g, 22%).

c) Heat-induced.

A sample of compound **11E** (0.3 g) was carefully melted at 110-120° for 4 hours. After cooling, crystallization from light petroleum yielded 0.2 g (80%) of **22**.

REFERENCES AND NOTES

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[5] Lit [4b] reports rearrangement of the only available isomer **6Z** by melting it with copper powder. In our hands, **6E** also gave the copper-catalyzed rearrangement into **8** through a prior *E* to *Z* isomerization.

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