

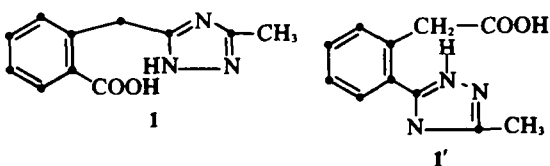
2-METHYL-S-TRIAZOLO[1,5-b]ISOQUINOLIN-5(10H)-ONE

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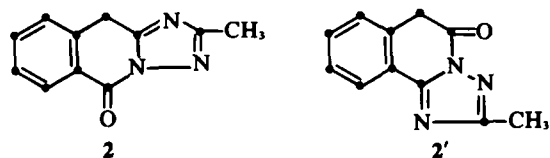
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Abstract—Acetamidrazone hydrochloride reacts with homophthalic anhydride to give 3-o-carboxybenzyl-5-methyl-1,2,4-triazole **1**, which can be cyclised to 2-methyl-s-triazolo[1,5-b] isoquinolin-5(10H)-one **2**. Reduction with lithium aluminium hydride gives 5,10-dihydro-2-methyl-s-triazolo[1,5-b] isoquinoline, while condensation with aromatic aldehydes gives 10-arylmethylene derivatives. Coupling with arenediazonium salts gives the 10-arylhydrazones of 5,10-dihydro-2-methyl-s-triazolo[1,5-b] isoquinoline-5,10-diones, while condensation with p-nitrosodimethylaniline gives the 10-imino derivative. Alkylation of **2** produces the corresponding 10,10-dialkyl derivatives.

Homophthalic anhydride reacted with acetamidrazone hydrochloride at 170° to yield 3-o-carboxybenzyl-5-methyl-1,2,4-triazole **1** as its hydrochloride, from which compound **1** was liberated by controlled neutralisation.

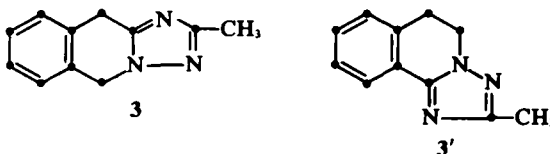


The NMR spectrum (DMSO- d_6) of **1** HCl showed peaks at δ 2.45 ppm (s, 3, CH₃), δ 4.40 ppm (s, 2, CH₂), δ 7.60 and δ 8.08 ppm (m, 4, aromatic protons), δ 9.82 ppm (s, 1, NH), and δ 10.40 ppm (s, 1, COOH). When compound **1**, HCl was heated in sodium acetate solution it yielded 2-methyl-s-triazolo[1,5-b] isoquinolin-5(10H)-one **2**. The angular isomer **2'** would result from the cyclisation of **1'**.



The NMR spectrum of **2** showed peaks at δ 2.80 ppm (s, 3-CH₃), δ 5.09 ppm (s, 2, CH₂), δ 7.90 and δ 8.56 ppm (m, 4, aromatic protons).

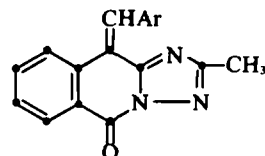
Compound **2** underwent ring-opening in boiling aqueous sodium hydroxide to yield **1**. Reduction of **2** gave an oxygen-free compound formulated as **3**. Compound **2'** would yield **3'**



The assignment of structure **3** (and hence the structures of its precursors), and not **3'**, to the reduction product is based on the comparison of the NMR spectra of **2** and **3**. (a) The inequality of the four aromatic protons in **2** (two multiplets centered at δ 7.90 ppm and δ 8.56 ppm) and on the other hand the equality of these protons after reduction in **3** (singlet at δ 7.48 ppm) indicates that the C=O group in **2** is more likely directly attached to the benzene ring. (b) The chemical shifts of the protons of the two methylene groups in **3** (two triplets centered at δ 4.49 and δ 5.48 ppm) are out of the normal region of two adjacent methylene groups. (c) The small coupling constant (J , 3 c/s) in the splitting of the signals of the protons of the two methylene groups in **3** is in the typical range for 1,4-coupling via a carbon-carbon double bond.¹

This formulation is in accord with the reaction of homophthalic anhydride with o-phenylenediamine,^{2,3} to give linear products.

Compound **2** condensed with aromatic aldehydes in refluxing acetic acid containing anhydrous sodium acetate to produce the 10-arylmethylene-2-methyl-s-triazolo[1,5-b] isoquinolin-5(10H)-one derivatives, **4**.

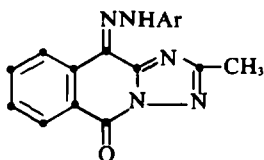


- 4a: Ar = C₆H₅
- 4b: Ar = C₆H₄NMe₂-p
- 4c: Ar = C₆H₄NO₂-o
- 4d: Ar = C₆H₄NO₂-p

Reduction of **4a** with zinc dust and acetic acid gave 10-benzyl-2-methyl-s-triazolo[1,5-b] isoquinoline-5(10H)-one (**7d**).

Compound **2** coupled with arenediazonium salts

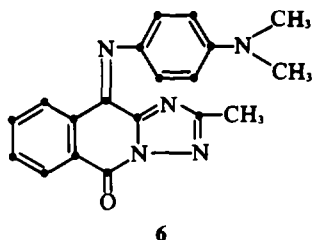
in pyridine to yield 5,10 - dihydro - 2 - methyl - s - triazolo [1,5-b] isoquinoline - 5,10 - dione 10 - arylhydrazones 5.



- 5a: Ar = C₆H₅,
 5b: Ar = C₆H₄CH₃-p
 5c: Ar = C₆H₄Cl-p
 5d: Ar = C₆H₄NO₂-p

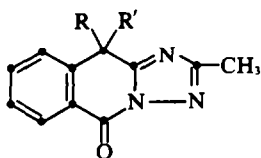
5a was also obtained by the condensation of α -phenylazo-homophthalic anhydride with acetamidrazone hydrochloride in dimethylformamide in presence of sodium acetate.

Condensation of 2 with p-nitrosodimethylaniline yielded 10 - (p - dimethylaminophenylimino) - 2 - methyl - s - triazolo [1,5-b] - isoquinolin - 5(10H) - one 6.



6

Compound 6 reacted with phenylhydrazine in acetic acid to give 5a. Reaction of 2 with halogenated compounds gave the 10,10-dialkyl derivatives 7. That the alkyl groups are attached to the same carbon atom, is evident from the NMR spectra of 7b and 7c, both showed a singlet for four protons at δ 4.07 and δ 4.74 ppm respectively.



- 7a: R = R' = C₂H₅,
 7b: R = R' = CH₂C₆H₅,
 7c: R = R' = CH₂COC₆H₅,
 7d: R = H; R' = CH₂C₆H₅

The dibenzyl derivative, 7b, was also obtained by the action of benzyl chloride on the monobenzylated compound 7d.

EXPERIMENTAL

M.p.s were taken on a Kofler apparatus and are uncorrected. Infrared (IR) spectra were determined as KBr pellets with a Perkin-Elmer Infracord 137 instrument.

NMR spectra were determined with a Perkin-Elmer R 12 A instrument. Ultraviolet (UV) spectra were obtained in DMF solution with a Perkin-Elmer spectrophotometer 402.

3 - (o - Carboxybenzyl) - 5 - methyl - s - triazole hydrochloride (1, HCl)

A mixture of 8.15 g of homophthalic anhydride and 5.47 g of acetamidrazone hydrochloride^{6,7} was heated in an oil bath at 170°C for 15 min. The product was crystallised from acetic acid to give 8 g (63%) of 1, HCl, m.p. 255° (charring); IR(KBr) 1695, 2750, 2950, 3150, 3350 cm⁻¹. Calc for C₁₁H₁₂ClN₃O₂: C, 52.03; H, 4.73; Cl, 14.00; N, 16.57. Found: C, 51.98; H, 4.92; Cl, 13.94; N, 16.58%.

3-(o-Carboxybenzyl)-5-methyl-s-triazole 1

A cold soln of 2.5 g of 1, HCl in 20 ml of water was treated gradually with NaHCO₃ (0.84 g) in 10 ml water. The solid that separated was collected and crystallised from methanol to give 1.7 g (79%) of 1, m.p. 202° with rapid resolidification: δ 2.3 ppm (s, CH₃), δ 4.45 ppm (s, CH₂), δ 7.39 and δ 7.90 ppm (m, aromatic protons), δ 12.1 ppm (broad s, NH and COOH). Calc for C₁₁H₁₁N₃O₂: C, 60.83; H, 5.07; N, 19.35. Found: C, 60.64; H, 5.10; N, 19.39%.

2-Methyl-s-triazolo [1,5-b]isoquinolin-5(10H)-one 2

(a) A solution of 5 g of 1, HCl in 50 ml of 10% aqueous sodium acetate was refluxed for 15 min when 3 g (75%) of 2 separated. Compound 2 was crystallised from DMF, m.p. 340°: λ_{\max} 267 nm (ϵ 8200), 322 nm (ϵ 6800), 349 nm (ϵ 9400); IR(KBr) 1666 cm⁻¹. Calc'd for C₁₁H₉N₃O (Mol Wt. 199.23): C, 66.33; H, 4.52; N, 21.11. Found: C, 65.96; H, 4.73; N, 21.16%; *m/e* 199.

(b) Heating 1 in boiling water, 2 was formed in 85% yield.

Action of NaOH on 2. A soln of 4 g of 2 in 50 ml of 5% NaOH was refluxed for 2 h, left to cool and acidified with dilute HCl to give 3 g (71%) of 1 m.p. and mixed m.p. 202°.

5,10 - Dihydro - 2 - methyl - s - triazolo [1,5-b]isoquinoline 3

To a suspension of 2.5 g of lithium aluminium hydride in 100 ml of dry ether and 100 ml of dry benzene, were added 2 g of finely powdered 2 and the mixture was refluxed for 6 h and left overnight. It was decomposed with ordinary ether then with ammonium chloride soln. The organic phase was separated and evaporated under reduced pressure. The residue (0.5 g; 25%) was crystallised from ethanol, to give 3 m.p. 195°. Calc for C₁₁H₁₁N₃: C, 71.35; H, 5.95; N, 22.70. Found: C, 70.97; H, 6.03; N, 22.60%.

10 - Arylmethylene - 2 - methyl - s - triazolo [1,5-b] isoquinolin - 5(10H) - ones 4a-d. General Procedure

A mixture of 2 g of 2, 3 g of anhydrous fused sodium acetate, 20 ml of acetic acid and an equimolecular amount of the appropriate aldehyde was refluxed for 2 h. The reaction mixture was cooled and poured into cold water. The precipitate formed was collected and crystallised from the proper solvent.

10 - Benzylidene - 2 - methyl - s - triazolo [1,5-b] isoquinolin-5(10H) - one 4a was obtained in 69% yield and crystallised from ethanol m.p. 140°. IR(KBr) 1725, 2950, 3100 cm⁻¹. Calc'd for C₁₈H₁₃N₃O: C, 75.43; H,

4.49; N, 14.53. Found: C, 75.17; H, 4.64; N, 14.69%. The 10-(*p*-dimethylaminophenyl methylene) analogue **4b** was crystallised from ethanol in 82% yield, m.p. 178°. Calcd for $C_{20}H_{18}N_4O$: C, 72.73; H, 5.44; N, 16.97. Found: C, 72.50; H, 5.55; N, 17.00%.

The 10-(*o*-nitrophenylmethylene)**4c** was crystallised from dilute acetic acid in 61% yield, m.p. 182°. Calc for $C_{18}H_{12}N_4O_3$: C, 65.06; H, 3.61; N, 16.86. Found: C, 65.02; H, 3.80; N, 16.83%.

The 10-(*p*-nitrophenylmethylene) analogue **4d** was crystallised from dimethylformamide in 89% yield, m.p. 262°. Calcd for $C_{18}H_{12}N_4O_3$: C, 65.06; H, 3.61; N, 16.86. Found: C, 64.82; H, 3.93; N, 17.08%.

10-Benzyl - 2 - methyl - s - triazolo[1,5-b]isoquinolin-5(10H) - one **7d**. Compound **4a** (2 g) was dissolved in 50 ml of acetic acid and treated with about 0.5 g of zinc dust. The soln was refluxed for 30 min (until a colourless solution was obtained) and filtered into cold water. The solid **7d** that separated was collected (91% yield) and crystallised from acetic acid, m.p. 259°. Calc for $C_{18}H_{15}N_3$: C, 74.74; H, 5.19; N, 14.53; Found: C, 74.76; H, 5.42; N, 14.41%.

5,10 - Dihydro - 2 - methyl - s - triazolo[1,5-b]isoquinoline - 5,10 - dione 10 - arylhydrazones **5**. General Procedure

Compound **2** (1 g) was dissolved in 20 ml of pyridine and cooled. The cold solution was treated dropwise with a cold solution of the diazonium salt and left for some time in the ice bath. The precipitate formed was collected and crystallised.

5,10 - Dihydro - 2 - methyl - s - triazolo[1,5-b]isoquinoline-5,10-dione 10-phenylhydrazone **5a** was obtained in 78% yield and crystallised from acetic acid, m.p. 235–6°; IR (KBr) 1725, 3030 cm^{-1} . Calcd. for $C_{17}H_{13}N_3O$: C, 67.33; H, 4.29; N, 23.10. Found: C, 67.28; H, 4.33; N, 23.30%. The 10-*p*-tolylhydrazone derivative **5b** was obtained in 80% yield and crystallised from dioxan, m.p. 231°. Calcd for $C_{18}H_{15}N_3O$: C, 68.14; H, 4.73; N, 22.09. Found: C, 67.98; H, 4.83; N, 22.01%. The 10-*p*-chlorophenylhydrazone analogue **5c** was obtained in 84% yield and crystallised from dioxan, m.p. 271°. Calc for $C_{17}H_{12}ClN_3O$: C, 60.44; H, 3.56; Cl, 10.55; N, 20.74. Found: C, 60.27; H, 3.60; N, 20.80%. The 10-*p*-nitrophenylhydrazone analogue **5d** was obtained in 84% yield and crystallised from dimethylformamide, m.p. 262°. Calcd for $C_{17}H_{12}N_4O_3$: C, 58.62; H, 3.45; N, 24.14. Found: C, 58.46; H, 3.50; N, 24.18%.

Reaction of phenylazohomophthalic anhydride and acetamidrazone hydrochloride

A mixture of 2.6 g of phenylazohomophthalic anhydride, 1.1 g of acetamidrazone hydrochloride, 2 g of fused anhydrous sodium acetate, and 10 ml of dry DMF was heated gently, with shaking to boiling. The reaction mixture (heating stopped) was then shaken occasionally for 10 min, and poured into cold water. The precipitate formed was collected and crystallised from acetic acid to give 2 g (66%) of **5a**, m.p. and m.m.p. 235°.

10 - (Dimethylaminophenylimino) - 2 - methyl - s - triazolo[1,5-b] - isoquinolin - 5(10H)-one **6**. A suspension

of 2 g of **2** in 50 ml of DMF was treated with a soln of 1.5 g of *p*-nitrosodimethylaniline in 50 ml of ethanol. The mixture was stirred for 15 min and diluted with water, 1.9 g (60%) of **6** was obtained and crystallised from benzene, m.p. 250°. Calcd for $C_{19}H_{17}N_3O$: C, 68.88; H, 5.14; N, 21.15. Found: C, 68.73; H, 5.03; N, 21.18%. IR(KBr) 1725 cm^{-1} .

Action of phenylhydrazine on **6**

A soln of 1.6 g of **6** and 0.4 g of phenylhydrazine in 20 ml of acetic acid was refluxed for 10 min. The orange crystals formed were collected and recrystallised from acetic acid to give 1 g (66%) of **5a**, m.p. and m.m.p. 235°.

10,10 - Dialkyl - 2 - methyl - s - triazolo[1,5-b]isoquinolin - 5 - (10H) - ones **7a-c**. General Procedure. About 2 g of **2** were dissolved in 50 ml of 4% aqueous alcoholic sodium carbonate soln. An excess (2.2 moles) of the alkyl halide was added, and the soln was refluxed for 3 h, left to cool and poured into cold water. The precipitate was collected, dried, and crystallised from the proper solvent.

10,10 - Diethyl - 2 - methyl - s - triazolo[1,5-b]isoquinolin - 5(10H) - one **7a**. It was obtained in 55% yield and crystallised from ethanol, m.p. 132°. Calcd for $C_{11}H_{17}N_3O$: C, 70.59; H, 6.67; N, 16.47. Found: C, 70.55; H, 6.74; N, 16.40%.

The 10,10-dibenzyl derivative **7b** was crystallised from ethanol in 84% yield, m.p. 183°; IR(KBr) 1725, 2940, 3030 cm^{-1} ; δ 2.88 ppm (s, CH_3), δ 4.07 ppm (s, two CH_2 groups), δ 6.80 and δ 8.26 ppm (m, aromatic protons). Calcd. for $C_{25}H_{21}N_3O$: C, 79.16; H, 5.54; N, 11.08. Found: C, 79.00; H, 5.67; N, 11.06%. **7b** was also obtained in 74% yield by the action of benzyl chloride on **7d** under the above conditions.

10,10-diphenacyl derivative **7c** was obtained in 76% yield and crystallised from acetic acid, m.p. 322°; δ 2.71 (s, CH_3), δ 4.72 ppm (s, two CH_2 groups) δ 7.62 ppm and 8.55 ppm (m, aromatic protons). Calcd. for $C_{27}H_{21}N_3O$: C, 74.48; H, 4.83; N, 9.65. Found: C, 74.26; H, 4.89; N, 9.36%.

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