Synthesis of 1,2,4-Triazolo[4',3':1,6]pyridazino[4,5-*b*]quinoline Derivatives

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This paper reports the synthesis of 10-phenyl-2*H*-pyridazino[4,5-*b*]quinoline-1-thione **10** and its further transformation into the hitherto unknown 12-phenyl-1,2,4-triazolo[4',3':1,6]pyridazino[4,5-*b*]quinoline **4**. 3-Carbethoxy-2-dichloromethyl-4-phenylquinoline **8** was reacted with hydrazine to give **9** which in turn was transformed by the Lawesson Reagent into the corresponding thione **10**. On treating **10** with anhydrous hydrazine, **11** was obtained and subsequently cyclized in the presence of formic or acetic acids to afford the tetracyclic derivatives **4a** and **4b**, respectively, in satisfactory yields. When 3-carbethoxy-2-chloromethyl-4-phenylquinoline **5** was reacted with hydrazine, compound **7** was the sole isolated product.

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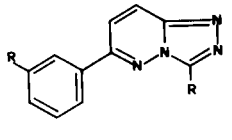
The present demand of models for ligand binding to benzodiazepine receptors has recently prompted the synthesis of a variety of new heterocyclic systems also structurally unrelated to the classic 1,4-benzodiazepines.

In this regard considerable attention has been drawn to the preparation of triazole-containing heterocycles, such as triazolopyridazines **1** [1] triazolophtalazines **2** [2] and triazolopyridazinoindoles **3** [3].

Following our research on polycyclic heteroaromatic compounds as potential psychotropic agents, we reported the synthesis of some 4-phenylquinoline derivatives and their affinities for 5-HT_1, 5-HT_2 and 5-HT_3 receptors [4].

Now, we wish to report the synthesis of a novel polycondensed ring system, namely 12-phenyl-1,2,4-triazolo[4',3':-1,6]pyridazino[4,5-*b*]quinoline **4**, involving at the same time the triazolopyridazine and the quinoline moieties, which may display affinities for benzodiazepine and 5-HT receptors.



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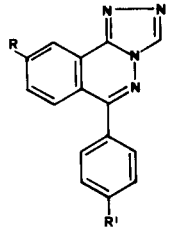

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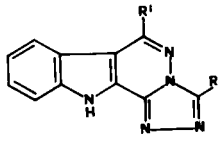

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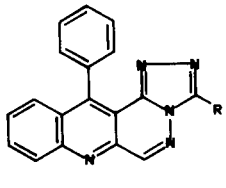

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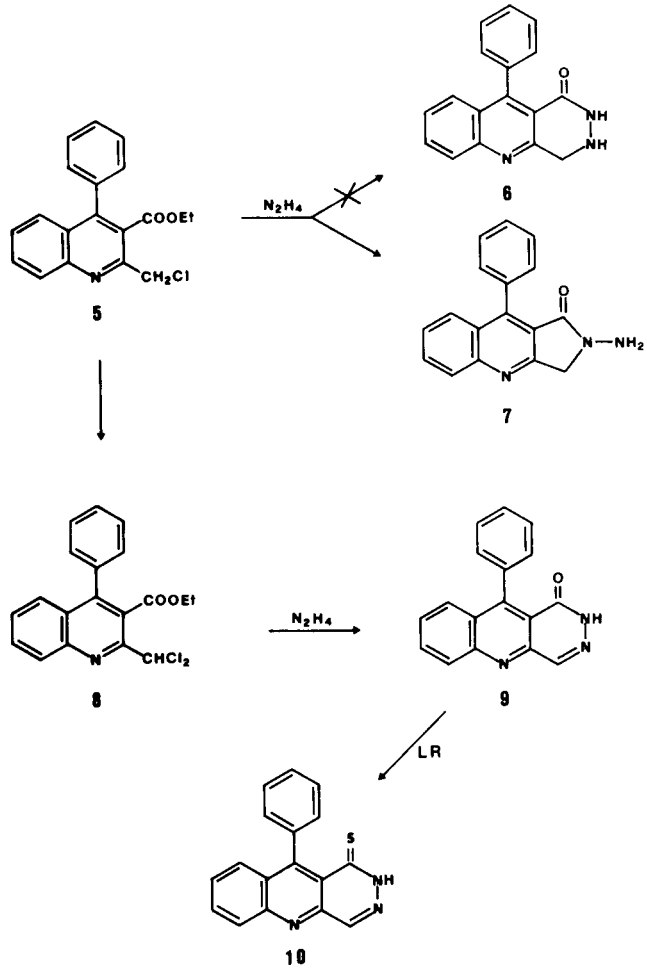
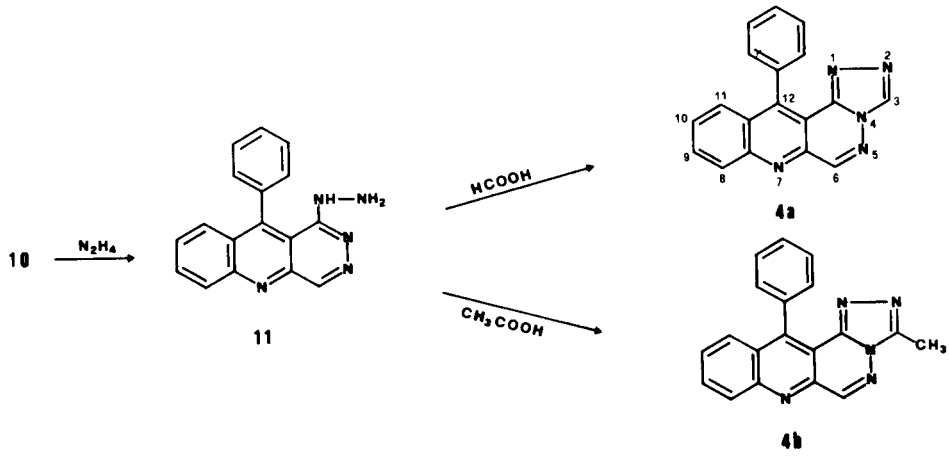
In a first attempt to obtain a pyridazino[4,5-*b*]quinoline nucleus, we examined the reaction of hydrazine hydrate with 3-carbethoxy-2-chloromethyl-4-phenylquinoline **5** prepared *via* Friedländer condensation between 2-aminobenzophenone and ethyl 4-chloroacetoacetate [4]. Spectroscopic analyses of the reaction product revealed that 2-amino-2,3-dihydro-9-phenyl-1*H*-pyrrolo[3,4-*b*]quinolin-1-one **7** had been obtained instead of the expected pyridazino derivative **6**. The structure of **7** was further confirmed by its ready condensation with carbonyl com-

Scheme I



Scheme II



pounds to give hydrazones. On the other hand, when the dichloro derivatives **8**, formed by treating **5** with *N*-chlorosuccinimide and benzoyl peroxide, was refluxed in ethanol in the presence of anhydrous hydrazine, **9** was obtained in 69% yield. This compound was cleanly transformed by the Lawesson Reagent into the corresponding thione **10**, which could by used without purification in the next step (Scheme I).

As depicted in Scheme II, the reaction of **10** with anhydrous hydrazine afforded the hydrazino derivative **11** in a good yield. While some literature reports claim the instability of similar derivatives [5], compound **11** is a stable, crystalline solid that can be stored for many weeks without appreciable decomposition. When refluxed with formic or acetic acids, **11** gave the triazolopyridazinoquinolines **4a** and **4b**, respectively, in 92% and 90% yields (Scheme II).

The structures of all compounds were fully confirmed by their spectral (ir and ^{1}H-nmr) and analytical data.

The biological properties of the new tricyclic and tetracyclic compounds here described are currently under evaluation and will be reported elsewhere.

EXPERIMENTAL

Melting points were determined in open capillaries on a Büchi apparatus and are uncorrected. Microanalyses were carried out on a Perkin-Elmer 240C Elemental Analyzer. Merck silica gel 60 (70-230 mesh) was used for column chromatography. The ir spectra were recorded in nujol mulls on a Perkin-Elmer 398 spectrophotometer. The ^{1}H-nmr spectra were recorded on a Varian XL 200 spectrometer in the indicated solvents. Chemical shifts are given in ppm from TMS as internal standard, and coupling constants (J) in Hz. Spectra and Elemental Analyses were performed by Dipartimento Farmaco Chimico Tecnologico - Università di Siena.

2-Amino-2,3-dihydro-9-phenyl-1*H*-pyrrolo[3,4-*b*]quinolin-1-one (**7**).

To a suspension of compound **5** (1.40 g, 4.3 mmoles) in methanol (25 ml), 98% hydrazine hydrate (1 ml) was added, and the mixture stirred at room temperature for a week. The precipitate which formed was collected by filtration, washed with cold methanol and recrystallized from ethanol-chloroform (1:1) to give the analytical sample melting at 216° dec (yield 68%); ir: 3420-3170 cm^{-1} (bs, NH_2), 1720 cm^{-1} (s, C=O); ^{1}H-nmr (DMSO-d_6): 4.63 (s, 2H, CH_2), 5.00 (s, 2H, NH_2), 7.39-7.86 (m, 8H, arom), 8.11 (d, 1H, J = 8.1, H-5).

Anal. Calcd. for $C_{17}H_{13}N_3O$: C, 74.16; H, 4.76; N, 15.27. Found: C, 73.97; H, 4.66; N, 15.00.

3-Carbethoxy-2-(dichloromethyl)-4-phenylquinoline (**8**).

To a solution of compound **5** (1.0 g, 3.1 mmoles) in carbon tetrachloride (20 ml), *N*-chlorosuccinimide (0.41 g, 3.1 mmoles) and benzoyl peroxide (in catalytic amount) were added portionwise. The mixture was refluxed for three days and then partially concentrated *in vacuo*. On cooling, succinimide was filtered off and the mother liquors evaporated to dryness. The residue, after chromatography, using chloroform-petroleum ether 40-60° (1:1) as eluent, gave a white solid (yield 90%). An analytical sample, melting at 76.5-78° was obtained after crystallization from ethanol; ir: 1710 cm^{-1} (s, C=O, ester); ^{1}H-nmr (deuteriochloroform): 0.82 (t, 3H, CH_2CH_3) 3.98 (q, 2H, CH_2CH_3), 7.32 (s, 1H, $CHCl_2$), 7.34-7.84 (m, 8H, arom), 8.28 (d, 1H, J = 9.0, H-8).

Anal. Calcd. for $C_{19}H_{15}Cl_2NO_2$: C, 63.34; H, 4.20; N, 3.89. Found: C, 63.06; H, 4.16; N, 3.88.

2*H*-10-Phenylpyridazino[4,5-*b*]quinolin-1-one (**9**).

To a suspension of compound **8** (0.7 g, 1.9 mmoles) in absolute ethanol (30 ml), anhydrous hydrazine (1 ml) was added. The reaction mixture was refluxed for two days. A yellow solid, precipitated on cooling, was collected by filtration and purified by chromatography eluting with chloroform-ethyl acetate (8:2).

A pale yellow solid was obtained (yield 69%) and recrystallized from toluene-DMF to give an analytical sample melting at 295-297°; ^{1}H-nmr (DMSO-d_6): 7.27-7.60 (m, 6H, arom), 7.66 (m, 1H, H-8), 7.98 (m, 1H, H-7), 8.22 (d, 1H, J = 8.6, H-6), 8.46 (s, 1H, H-4), 12.41 (s, 1H, NH).

Anal. Calcd. for $C_{17}H_{11}N_3O$: C, 74.71; H, 4.06; N, 15.38. Found: C, 74.80; H, 4.16; N, 15.01.

2*H*-10-Phenylpyridazino[4,5-*b*]quinoline-1-thione (**10**).

2,4-Bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide, (Lawesson Reagent) (1.1 g, 2.7 mmoles) was added por-

tionwise to a hot solution of **9** (1.1 g, 4.0 mmoles) in anhydrous toluene (30 ml). The reaction mixture was refluxed for 1 hour, and the resulting orange solution, after partial removal of the solvent *in vacuo*, was allowed to cool to room temperature. The crude product (yield 85%) was filtered, washed with a little amount of toluene and recrystallized from absolute ethanol, mp 279° dec; ir: 3125 cm^{-1} (s, NH), 1350 cm^{-1} (s, C=S); ^{1}H-nmr (DMSO-d_6): 7.18-7.49 (m, 6H, arom), 7.64 (m, 1H, H-8), 8.01 (m, 1H, H-7), 8.24 (d, 1H, J = 8.3, H-6), 8.77 (s, 1H, H-4), 13.93 (s, 1H, NH).

Anal. Calcd. for $C_{17}H_{11}N_3S$: C, 70.56; H, 3.83; N, 14.52. Found: C, 70.44; H, 3.77; N, 14.40.

1-Hydrazino-10-phenylpyridazino[4,5-*b*]quinoline (**11**).

To a suspension of compound **10** (0.87 g, 3 mmoles) in absolute ethanol (30 ml) anhydrous hydrazine (5 ml) was added and the reaction mixture heated to reflux for 1 hour. The product, which crystallized on cooling after partial removal of the solvent *in vacuo*, was collected by filtration and washed with absolute ethanol. A recrystallization from absolute ethanol gave an analytical sample (yield 70%), melting at 213° dec; ir: 3125-3300 cm^{-1} (bs, NH-NH_2); ^{1}H-nmr (DMSO-d_6): 5.20 (bm, 2H, NH_2), 7.00-7.60 (m, 7H, arom), 7.66 (s, 1H, H-4), 7.71 (m, 1H, H-7), 8.00 (d, 1H, J = 8.3, H-6), 10.40 (bm, 1H, NH).

Anal. Calcd. for $C_{17}H_{13}N_5$: C, 71.06; H, 4.56; N, 24.38. Found: C, 71.28; H, 4.52; N, 24.28.

12-Phenyl-1,2,4-triazolo[4', 3':1,6]pyridazino[4,5-*b*]quinoline (**4a**).

A mixture of compound **11** (0.32 g, 1 mmole) and formic acid (5 ml) was heated under reflux for 0.5 hour. The solvent was removed *in vacuo* and the residual solid was suspended in ethanol (15 ml), filtered, washed with water, dried and finally recrystallized from toluene (yield 92%), mp >300°; ^{1}H-nmr (DMSO-d_6): 7.40-7.70 (m, 6H, arom), 7.80 (m, 1H, H-10), 8.02 (m, 1H, H-9), 8.35 (d, 1H, J = 8.3, H-8), 9.13 (s, 1H, H-6), 9.50 (s, 1H, H-3).

Anal. Calcd. for $C_{17}H_{11}N_5$: C, 72.72; H, 3.73; N, 23.55. Found: C, 72.80: H, 3.75; N, 23.45.

3-Methyl-12-phenyl-1,2,4-triazolo[4',3':1,6]pyridazino[4,5-*b*]quinoline (**4b**).

A mixture of compound **11** (0.40 g, 1.2 mmoles) and glacial acetic acid (5 ml) was refluxed for 40 minutes. The reaction mixture was poured onto crushed ice and the precipitate collected by filtration, washed with water, dried and recrystallized from toluene (yield 90%) mp >300°; ^{1}H-nmr (DMSO-d_6): 2.64 (s, 3H, CH_3), 7.40-7.74 (m, 6H, arom), 7.82 (m, 1H, H-10), 8.05 (m, 1H, H-9), 8.37 (d, 1H, J = 8.7, H-8), 9.13 (s, 1H, H-6).

Anal. Calcd. for $C_{18}H_{13}N_5$: C, 73.30; H, 4.20; N, 22.49. Found: C, 73.47; H, 4.27; N, 22.26.

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