AN ALTERNATIVE SYNTHESIS OF DIPEPTIDO-AMINOBENZOPHENONE AND NOVEL HETEROCYCLIC FORMATIONS OF RING-OPENED 1,4-BENZODIAZEPINE DERIVATIVES[1]

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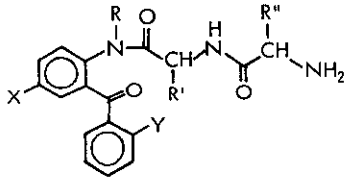
Abstract — An alternative synthesis of Gly-Gly-N-methylaminobenzophenone (1a) via iodoacetyl glycylaminobenzophenone (2) is described. Novel ring closures of 2 and cyano derivative 3 are also reported.

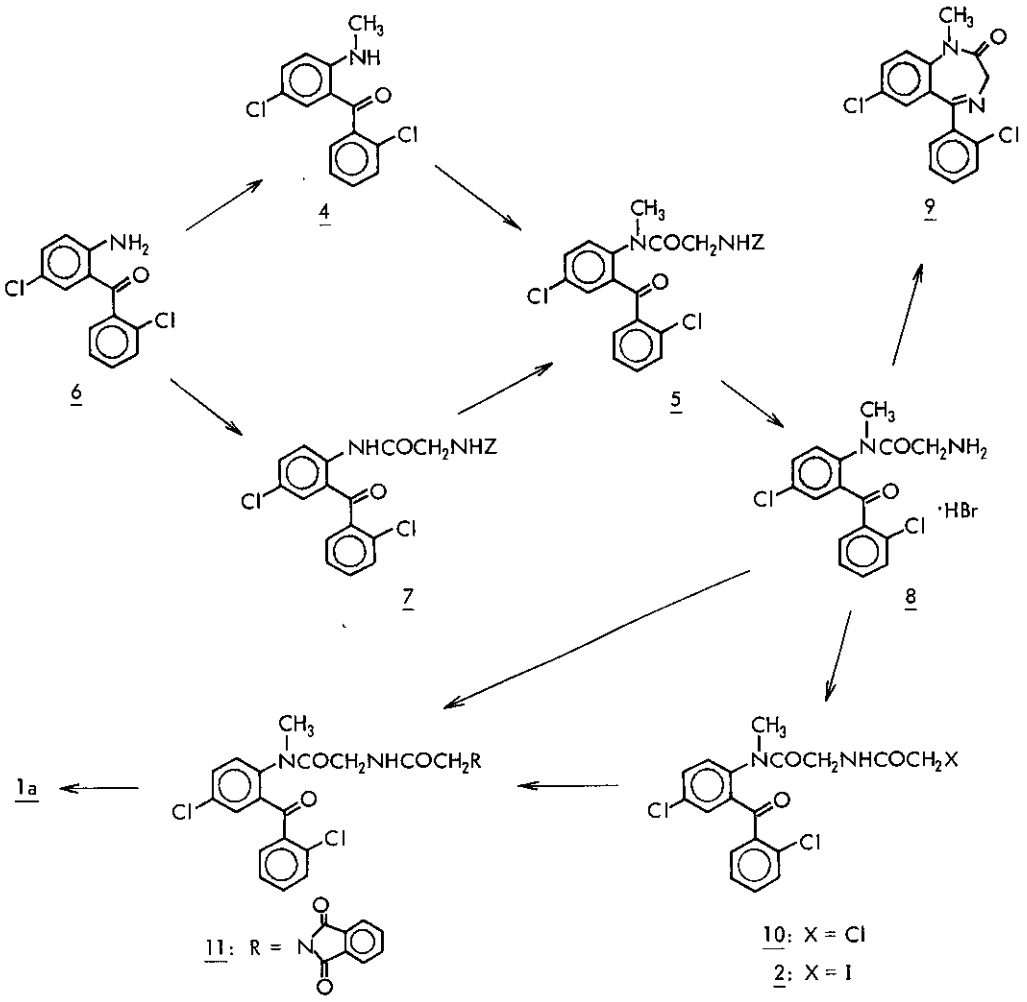
The 1,4-benzodiazepines have been known as potent tranquilizing, anticonvulsant, and hypnotic agents. Recently, we have prepared peptido-aminobenzophenones (1) as a novel class of ring-opened derivatives of 1,4-benzodiazepines.[1,2]

We wish to report an alternative synthesis of pharmacologically interesting 4-chloro-2-(o-chlorobenzoyl)-N-methyl-N^{α}-glycylglycinanilide (1a)[3] and novel ring closures of iodoacetylglycylaminobenzophenone (2) and cyanoacetylglycylaminobenzophenone (3) which give heterocyclic compounds.



1 1a: R = CH_3, R' = R" = H, X = Y = Cl

Z-Glycine was activated by $SOCl_2$ in hexamethylphosphoramide (HMPA)[4] at -8~-5° and coupled with N-methylaminobenzophenone (4) to give Z-glycyl-N-methylaminobenzophenone (5), mp 90-92°, in 81% yield. Compound 4 was readily obtained from aminobenzophenone (6) by treatment with KOH in DMF or DMSO followed by the action of CH_3I at room temperature in 89-91% yield. This method is simpler and safer than other methods via tosyl amide[5] or using sodium hydride.[6] Coupling of 6 with Z-glycine by $SOCl_2$/HMPA at -8~-5°C gave Z-glycylaminobenzophenone (7), mp 146-147°, in 80% yield. N-Methylation of 7 by the action of CH_3I after treatment with sodium hydride (50% oil dispersion) in DMF at room temperature also gave 5 in 86.5% yield. Deblocking of 5 with 20%

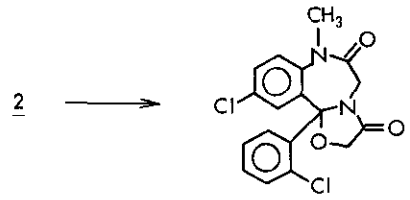


HBr-AcOH at room temperature gave glycyl-N-methylaminobenzophenone hydrobromide (8), mp 156-159°, in 96.5% yield.

Since glycyl-N-methylaminobenzophenone hydrobromide (8) spontaneously cyclized on neutralization giving 1,4-benzodiazepine (9),[7] chloroacetylation of 8 was carried out by the action of chloroacetyl chloride in DMF or HMPA at room temperature in the absence of base and the coupling product 10, mp 134-136°, was obtained in 89% yield without concomitant production of the cyclized compound 9. Chloroacetyl compound 10 was converted into the iodo derivative 2, mp 168.5-169.5°, by the action of KI in acetone with refluxing. Reaction of 2 with potassium phthalimide in DMF at room temperature gave Pht-Gly-Gly-N-methylaminobenzophenone (11)[1] in 98% yield. Compound 11 was also obtained from 8 by the action of phthalylglycyl chloride in DMF at room temperature in the absence of base in 93.5% yield. Since the phthalyl group in 11 is

readily removed by hydrazinolysis,[1] this is an alternative synthesis of 1a.

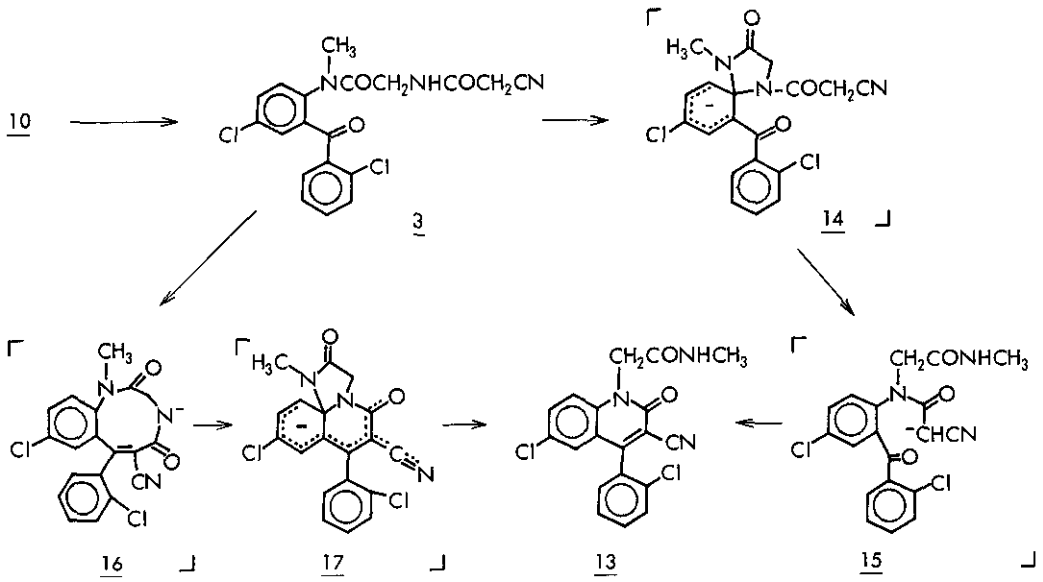
An attempt to methylate 2 by the action of CH_3I after treatment with sodium hydride in DMF at room temperature gave compound 12, mp 198-199°, in 66% yield, instead of the N-methylated compound. Elemental analysis indicated that 12 had one HI less than 2. IR of 12 showed two amido carbonyl bands at 1720 and 1675 cm^{-1} (Nujol). NMR ($CDCl_3$) of 12 exhibited the following signals: δ 2.58 (3H, s, N-CH_3), 3.42 and 4.62 (2H, ABq, J = 14 Hz, N-CH_2-CO), 4.38 (2H, s, O-CH_2-CO). These data suggested the structure of 12 to be oxazolo[3,2-d][1,4]benzodiazepine. This type of heterocycle was previously obtained from 1,4-benzodiazepine through several steps via a 1,3-dipolar cycloaddition product with nitrile oxide.[8] Note that double cyclization of 2 occurred readily and 12 was obtained in one step. This reaction may be explained as follows: the amide N-anion of 2 attacked the carbon atom in the benzoyl carbonyl group and the O-anion formed attacked the methylene group to remove the terminal iodine atom giving the tricyclic compound 12.



2 ⟶ 12

Cyanoacetyl derivative 3, mp 139-140°, was prepared from 10 by the action of KCN and KI in DMF at room temperature in 59.4% yield. When 3 was treated with sodium hydride in DMF at room temperature, compound 13, mp 191-193°, was obtained in 73% yield. Elemental analysis indicated that 13 contained one H_2O less than 3. The UV spectrum showed a pattern characteristic of quinolone derivatives[9] [λ_{max}^{EtOH} 216, 245, 292, 303, 375 nm (log ε 4.68, 4.62, 4.02, 3.97, 3.78)]. The IR (Nujol) spectrum showed a C≡N band at 2235 cm^{-1} with a stronger intensity than 3 (2260 cm^{-1}). NMR spectroscopy ($CDCl_3$) gave the following signals: δ 2.82 (3H, d, J = 5 Hz, NHCH_3), 4.87 and 5.72 (2H, ABq, J = 16 Hz, CH_2). These data strongly supported a quinolone structure having a conjugated cyano group and a methylamidomethyl group for 13.

An N→N Smiles rearrangement in halogenoacetamide was reported in nitrobenzene[10] and thiophene[11] derivatives. Possible mechanisms forming 13 from 3 may be explained as follows: a) intramolecular nucleophilic aromatic rearrangement of amide N-anion of 3 formed 15 via 14 then dehydration gave 13, or b) dehydration of 3 between active methylene and benzoyl carbonyl groups gave 16, followed by a transannular nucleophilic aromatic rearrangement facilitated by activation of the aromatic ring by conjugated cyano and amido groups giving 13.[12]



REFERENCES AND NOTES

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12. Correct combustion analyses were obtained for all new compounds whose melting points (uncorrected) are given.

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