

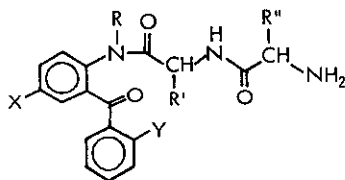
AN ALTERNATIVE SYNTHESIS OF DIPEPTIDO-AMINOBENZOPHENONE AND NOVEL
HETEROCYCLIC FORMATIONS OF RING-OPENED 1,4-BENZODIAZEPINE DERIVATIVES¹

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

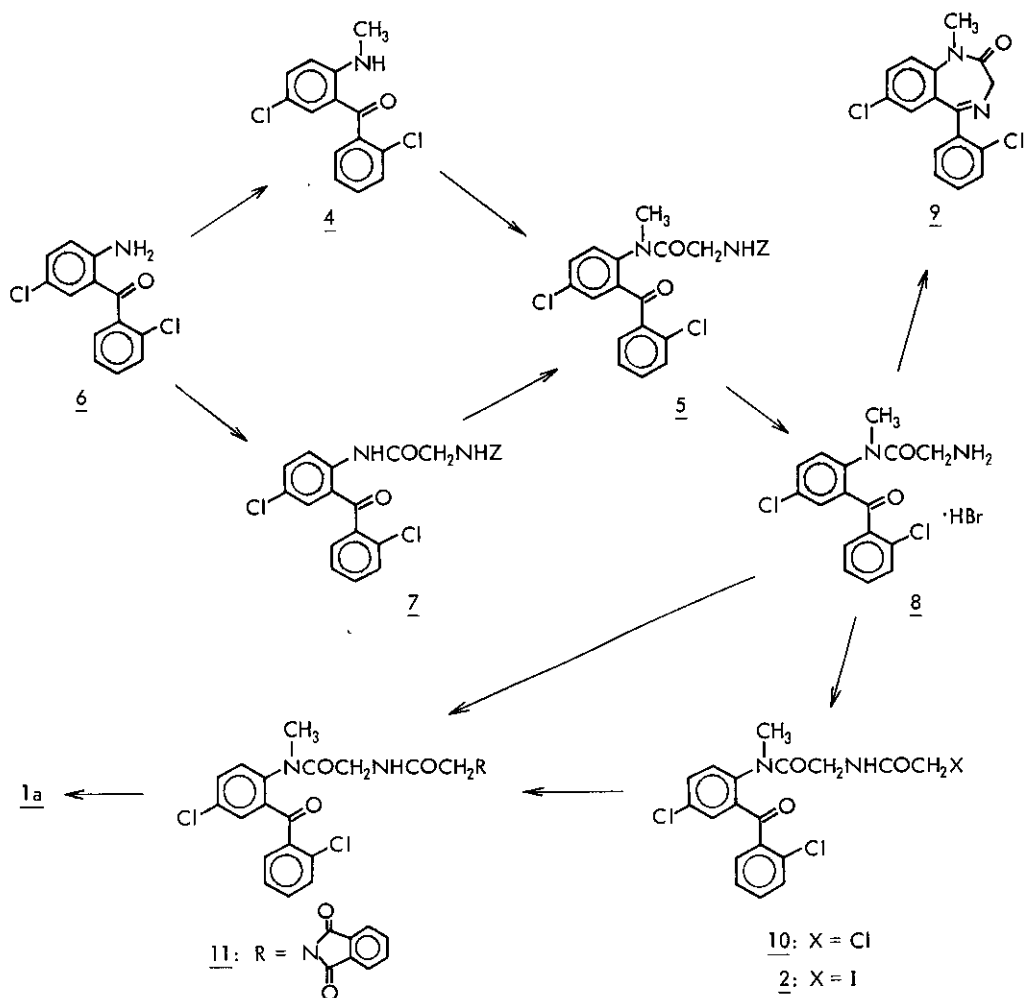
The 1,4-benzodiazepines have been known as potent tranquilizing, anticonvulsant, and hypnotic agents. Recently, we have prepared peptido-aminobenzophenones (1) as a novel class of ring-opened derivatives of 1,4-benzodiazepines.^{1,2}

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 iodoacetyl-glycyaminobenzophenone (2) and cyanoacetyl-glycyaminobenzophenone (3) which give heterocyclic compounds.



1 1a: R = CH₃, R' = R'' = H, X = Y = Cl

Z-Glycine was activated by SOCl₂ 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 CH₃I at room temperature in 89-91% yield. This method is simpler and safer than other methods *via* tosyl amide⁵ or using sodium hydride.⁶ Coupling of 6 with Z-glycine by SOCl₂/HMPA at -8~-5°C gave Z-glycyaminobenzophenone (7), mp 146-147°, in 80% yield. N-Methylation of 7 by the action of CH₃I 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%

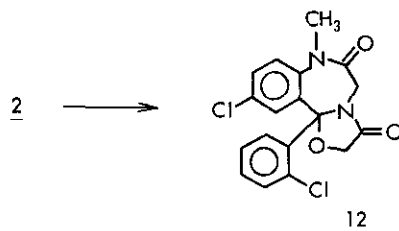


HBr-AcOH at room temperature gave glycyl-N-methylaminobenzophenone hydrobromide (**8**), mp 156-159°, in 96.5% yield.

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

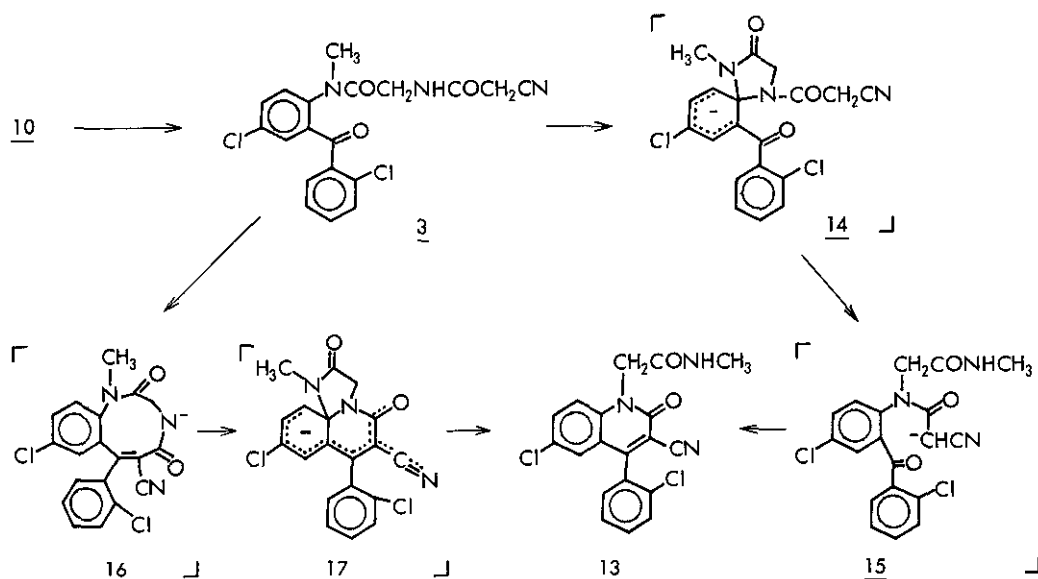
readily removed by hydrazinolysis,¹ this is an alternative synthesis of 1a.

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, $\text{N-CH}_2\text{-CO}$), 4.38 (2H, s, $\text{O-CH}_2\text{-CO}$). 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.



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 derivatives⁹ [$\lambda_{\text{max}}^{\text{EtOH}}$ 216, 245, 292, 303, 375 nm ($\log \epsilon$ 4.68, 4.62, 4.02, 3.97, 3.78)]. The IR (Nujol) spectrum showed a $\text{C}\equiv\text{N}$ 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 $\rightarrow$ N Smiles rearrangement in halogenoacetamide was reported in nitrobenzene¹⁰ and thiophene¹¹ 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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