Quinazolines and 1,4-Benzodiazepines. LI. (1) The Synthesis of the *t*-Butyl Analog of Diazepam

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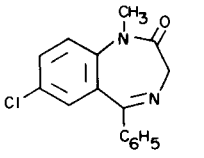
Our interest in diazepam **1** (2), and its biological activity induced us to synthesize a closely related compound which would be expected to be metabolized in a different manner. Since the 1-desmethyl derivative **2** is a major metabolite (3) of diazepam, it seemed of interest whether or not its formation is a prerequisite for the biological activity of diazepam.



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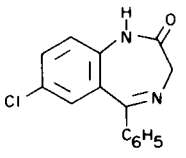

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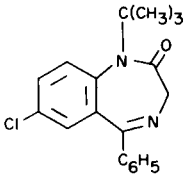


3

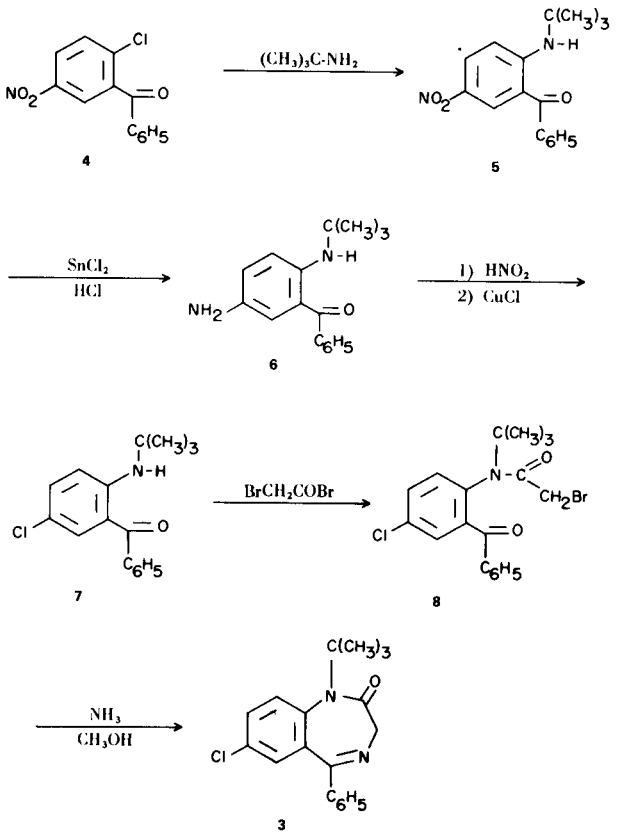
Since it is known that *t*-butyl ethers are not metabolized in the same manner as methyl ethers (4a,b) (*t*-butyl ethers remain intact whereas methyl ethers are readily dealkylated), it was decided to prepare the *t*-butyl homolog **3** of diazepam so that its metabolism and biological activity could be compared with that of **1** (5). This paper describes the chemical part of the synthesis of compound **3**, whereas, the metabolic studies will be reported, after completion, by M. Schwartz and co-workers.

The preparation of **3** turned out to be quite complicated since the *t*-butyl group could not be introduced directly into **2**.

The synthesis was, therefore, carried out as outlined below.

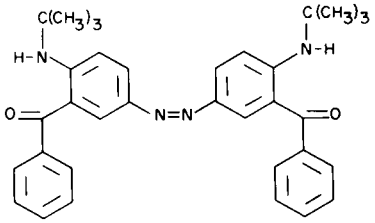
The reaction of 2-chloro-5-nitrobenzophenone **4** with an excess of *t*-butylamine in a Parr bomb at 200° for 24 hours led to a 77% yield of 2-*t*-butylamino-5-nitrobenzophenone **5**. The reduction of the nitro group to an amine

Scheme I



proceeded smoothly with stannous chloride. The Sandmeyer reaction of **6** with cuprous chloride to give the product **7** (6) led, in some cases, quite unexpectedly to large amounts of the azo compound **9**, even in concentrated acid medium, conditions which normally suppress coupling reactions (7).

The structure of **9** was substantiated by elemental analysis and mass spectral studies which gave the correct molecular weight and showed the absence of chlorine. The separation of **9** from **7** could be affected by column chromatography.



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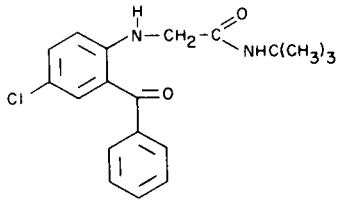
The bromoacetylation of **7** with bromoacetyl bromide in refluxing benzene led to high yields of **8**. The reaction of **8** with methanolic ammonia at room temperature yielded a mixture of the desired benzodiazepine **3** and an impurity which after separation by thick layer chromatography was characterized as the rearranged amide **10**.



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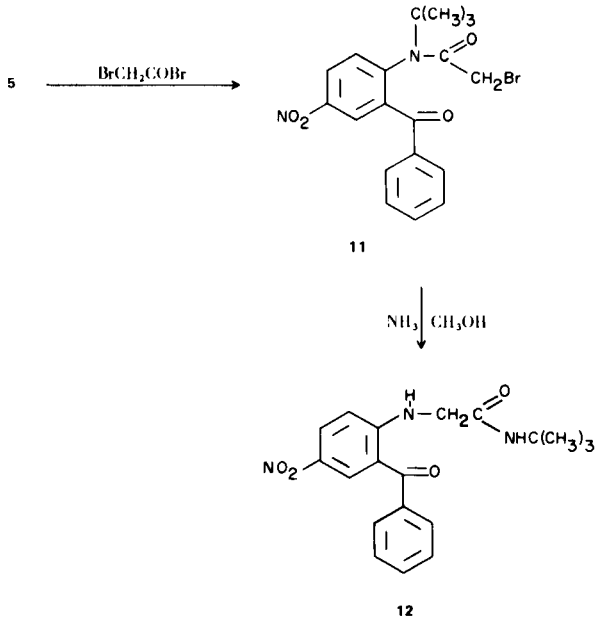
The structure of **10** was supported by all spectra and by elemental analysis. Interestingly, the use of hexamethyl phosphoric triamide as solvent in place of methanol led only to the formation of **10**; no benzodiazepine **3** could be detected.

This rearrangement was subsequently shown to be general for the reaction of 2-bromoacetanilides with primary amines (8).



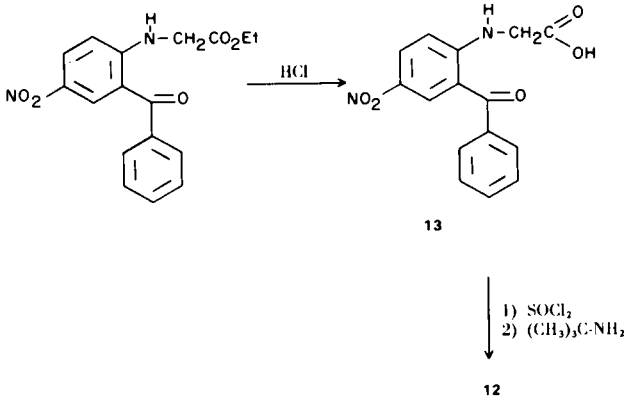
11

12

Another approach to **3** which was considered, was the conversion of **5** by the usual reaction sequence into the 7-nitrobenzodiazepinone which by reduction and Sandmeyer reaction was expected to yield the desired product. This, however, was not successful, since treatment of **11** with methanolic ammonia led in every case only to the rearranged product **12**.

All spectra supported the structure **12**, and it was proved conclusively by an independent synthesis as shown in Scheme II.

Scheme II



13

12

EXPERIMENTAL (9)

2-*t*-Butylamino-5-nitrobenzophenone (**5**).

A mixture of 2-chloro-5-nitrobenzophenone (**4**) (130 g., 0.5 mole) and *t*-butylamine (300 ml., 2.9 moles) was heated at 200° in a Parr bomb for 24 hours. The mixture was partitioned between methylene chloride and aqueous sodium bicarbonate. The aqueous phase was extracted several times with methylene chloride, the organic solutions combined and washed with water, dried (magnesium sulfate), and concentrated to give 125 g. of solid product which crystallized from ethanol to give 114 g. (77%) of **5**, m.p. 157-158°.

Anal. Calcd. for $C_{17}H_{18}N_2O_3$: C, 68.44; H, 6.08; N, 9.39. Found: C, 68.51; H, 6.21; N, 9.55.

2-*t*-Butylamino-5-aminobenzophenone (**6**).

A solution of 6.0 g. (20 mmoles) of **5** in 80 ml. of hot glacial acetic acid was added portionwise to a stirred solution of 15 g. (66 mmoles) of stannous chloride in 100 ml. of acetic acid and 20 ml. of 6 *N* hydrochloric acid. The resulting mixture was stirred at room temperature for 66 hours and then poured into 150 ml. of ice water. The solution was brought to *p*H 10 with 10 *N* sodium hydroxide and extracted thoroughly with methylene chloride. After washing with water, the organic phase was dried (magnesium sulfate) and concentrated to give 5.0 g. (93%) of a dark red oil which slowly crystallized. Crystallization from ether and hexane gave red-orange needles, m.p. 112-112.5°.

Anal. Calcd. for $C_{17}H_{20}N_2O$: C, 76.09; H, 7.51; N, 10.44. Found: C, 76.39; H, 7.59; N, 10.40.

2-*t*-Butylamino-5-chlorobenzophenone (**7**).

A solution of 10 g. (37.4 mmoles) of **6** in 65 ml. of 3 *N* hydrochloric acid was stirred in an ice bath and a solution of 2.5 g. (36 mmoles) of sodium nitrite in 65 ml. of water was added drowise keeping the temperature below 5°. After the addition was complete, the mixture was poured into a solution of 6.5 g. (66 mmoles) of cuprous chloride in 65 ml. of 6 *N* hydrochloric acid and stirred at 0° for 1 hour. After warming on the steam bath for 15 minutes, the solution was diluted with 2 volumes of water, made basic with concentrated ammonium hydroxide and extracted with methylene chloride. The organic layer was washed with water, dried (magnesium sulfate) and concentrated to give 11 g. of a viscous black oil. Chromatography over neutral alumina (benzene as eluent) gave 10.3 g. (96%) of orange oil, which slowly crystallized. Recrystallization from ether and petroleum ether (b.p. 30-60°) gave yellow prisms, m.p. 64-66°. The picrate was prepared and recrystallized from ethanol to provide the analytical sample, m.p. 153-154°.

Anal. Calcd. for $C_{23}H_{21}ClN_4O_8$: C, 53.44; H, 4.09; N, 10.84. Found: C, 53.63; H, 3.98; N, 10.81.

2′-Benzoyl-4′-chloro-*N*-*t*-butyl-2-bromoacetanilide (**8**).

Bromoacetyl bromide (9.5 ml., 109 mmoles) was added to a solution of **7** (8.9 g., 31 mmoles) in 150 ml. of benzene. The mixture was heated to reflux whereupon the color turned to black-green. As hydrobromic acid was evolved, the color changed to purple and finally to red after 2 hours. Refluxing was continued for a total of 4 hours and then the solution was cooled, diluted with benzene, washed with 3 *N* sodium hydroxide, sodium chloride, dried (magnesium sulfate), and concentrated to give 11.3 g. of solid which was recrystallized from heptane to give 7.6 g. (60%), m.p. 157-159°. A second crop yielded 3.0 g. (24%), m.p. 148-153°. Further recrystallization from methylene chloride and petroleum ether (b.p. 30-60°) gave colorless prisms, m.p. 161-162°.

Anal. Calcd. for $C_{19}H_{19}BrClNO_2$: C, 55.83; H, 4.69; N, 3.43. Found: C, 56.11; H, 4.82; N, 3.43.

1-*t*-Butyl-7-chloro-1,3-dihydro-5-phenyl-1,4-(2*H*)-benzodiazepin-2-one (**3**).

A solution of 4.0 g. (9.8 mmoles) of **8** in 125 ml. of 11% ammonia in methanol and 125 ml. of ether was stirred at room temperature for 72 hours. Additional 11% ammonia in methanol (25 ml.) was added and the solution stirred for 48 hours. After removal of the solvents *in vacuo*, the residue was partitioned between methylene chloride and saturated sodium bicarbonate. The organic layer was washed with water, dried (magnesium sulfate), and concentrated to give 3.6 g. of a yellow foam. Purification of 600 mg. was effected by thick layer chromatography (hexane:ether 1:1 as eluent) to give 377 mg. (67%) of the benzodiazepine **3**. The minor product was assigned the structure **12** on the basis of the Rf value. Recrystallization of **3** from pentane gave colorless prisms, m.p. 100-103°.

Anal. Calcd. for $C_{19}H_{19}ClN_2O$: C, 69.83; H, 5.86; N, 8.57. Found: C, 69.88; H, 5.92; N, 8.64.

5,5′-Axobis(2-*t*-butylaminobenzophenone) (**9**).

In attempts to reproduce the preparation of **7**, thin layer chromatography showed that substantial amounts of a contaminant were formed. This by-product was isolated by column chromatography and recrystallized from benzene and hexane to give orange plates, m.p. 209-211°. The mass spectrum gave a molecular ion at m/e 532 (theory m/e 532) and showed that no chlorine was present.

Anal. Calcd. for $C_{34}H_{36}N_4O_2$: C, 76.66; H, 6.81; N, 10.52. Found: C, 77.04; H, 6.85; N, 10.52.

N^2-(2-Benzoyl-4-chlorophenyl)-*N*-*t*-butylglycinamide (**10**).

The bromoacetanilide **8** (4.0 g., 10 mmoles) was dissolved in 100 ml. of hexamethylphosphoric triamide and stirred at 0°. Ammonia was bubbled in slowly for 4 hours and the resulting solution stirred overnight at room temperature. After dilution with 500 ml. of ether, the solution was washed with 5 x 100 ml. portions of 50% sodium chloride to remove hexamethylphosphoric triamide, dried (magnesium sulfate), and concentrated to give 3.3 g. of a yellow gum which was chromatographed on 40 g. of neutral alumina (ethyl acetate as eluent) to give 2.5 g. (77%) of solid product, m.p. 147-149°. Recrystallization from heptane gave the analytical sample, m.p. 147-149°.

Anal. Calcd. for $C_{19}H_{21}ClN_2O_2$: C, 66.18; H, 6.14; N, 8.12. Found: C, 65.86, 65.79; H, 6.09, 6.21; N, 8.09, 8.21.

2′-Benzoyl-4′-nitro-*N*-*t*-butyl-2-bromoacetanilide (**11**).

A mixture of 5.0 g. (16.8 mmoles) of **5**, 3.8 ml. (43.5 mmoles) of bromoacetyl bromide and 80 ml. of benzene was refluxed for 48 hours and concentrated *in vacuo*. The residue was dissolved in methylene chloride and washed with sodium bicarbonate. After drying (magnesium sulfate), the organic phase was concentrated and the solid product recrystallized from ethanol to give 5.8 g. (82%), m.p. 202-203°.

Anal. Calcd. for $C_{19}H_{19}BrN_2O_4$: C, 54.43; H, 4.57; N, 6.68. Found: C, 54.48; H, 4.47; N, 6.71.

N^2-(2-Benzoyl-4-nitrophenyl)-*N*-*t*-butylglycinamide (**12**).

A heterogeneous mixture of 4.8 g. (11.5 mmoles) of **11**, 150 ml. of 11% ammonia in methanol, and 200 ml. of ether was stirred at room temperature for 72 hours, at which time solution was complete. After the addition of 50 ml. of 11% ammonia in methanol, the solution was stirred for 48 hours and the solvents removed *in vacuo*. The residue was dissolved in methylene chloride, washed with aqueous sodium bicarbonate; the organic phase was dried (magnesium sulfate), concentrated and the yellow foam obtained was recrystallized from benzene and petroleum ether (b.p. 30-60°) to give 3.3 g. (81%) of **12**, m.p. 175-176°.

Anal. Calcd. for $C_{19}H_{21}N_3O_4$: C, 64.21; H, 5.96; N, 11.83. Found: C, 64.31; H, 5.96; N, 11.89.

Preparation of **12** from **13**.

A solution of 500 mg. (1.64 mmoles) of **13** in 7 ml. of thionyl chloride was refluxed for 2 hours. The solution was cooled, concentrated *in vacuo* and the excess thionyl chloride chased with benzene. The solid product was washed with petroleum ether (b.p. 30-60°) to give 500 mg. (96%) of crude acid chloride, m.p. 125-128° dec., suitable for use in the next step. The analytical sample was prepared from benzene and hexane, m.p. 128.5-130° dec.

Anal. Calcd. for $C_{15}H_{11}ClN_2O_4$: C, 56.53; H, 3.48; N, 8.79. Found: C, 56.81; H, 3.50; N, 8.55.

To a mixture of 5 ml. of *t*-butylamine, 0.31 ml. of 1 *N* sodium hydroxide, and 4 ml. of water, was added 100 mg. (0.31 mmole) of the acid chloride, in portions, with vigorous shaking. After the addition was complete, water was added and extracted with ether. The ether extracts were washed with saturated sodium chloride, dried (magnesium sulfate), and concentrated. The residue was recrystallized from benzene and petroleum ether (b.p. 30-60°) to give 93 mg. (84%) of **12**. All physical properties were identical with the product obtained by the ammonolysis of **11**.

N^2-(2-Benzoyl-4-nitrophenyl)glycine (**13**).

A mixture of 2.0 g. (6.1 mmoles) of N^2-(2-benzoyl-4-nitrophenyl)glycine ethyl ester, 10 ml. of 6 *N* hydrochloric acid, and 15 ml. of dioxane was refluxed for 3 hours. After cooling, the solution was diluted with ether, washed once with water, then with a large volume of 2 *N* sodium hydroxide (the acidic product is sparingly soluble in sodium hydroxide). The basic solution was washed with ether, made acidic with 12 *N* hydrochloric acid, and filtered to give 1.9 g. of yellow solid which was recrystallized from acetic acid and water to give 1.4 g. (76%) of **13**, m.p. 214-215°, as yellow needles.

Anal. Calcd. for $C_{15}H_{12}N_2O_5$: C, 60.00; H, 4.03; N, 9.33. Found: C, 60.33; H, 3.99; N, 9.48.

Acknowledgment.

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(5) This project was suggested by Dr. J. J. Burns.

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(7) See for example: R. Wistar and P. D. Bartlett, *J. Am. Chem. Soc.*, 63, 413 (1941). C. R. Hauser and D. S. Breslow, *ibid.*, 63, 418 (1941).

(8) N. W. Gilman, P. Levitan, and L. H. Sternbach, *Tetrahedron Letters*, 4121 (1970).

(9) All melting points were taken on a calibrated Thomas-Hoover capillary melting point apparatus. The nmr spectra were determined on a Varian A-60 instrument, the ir spectra were determined on a Beckmann IR-9 instrument and the mass spectra were determined on a CEC 21-110B instrument. All spectral data were in agreement with the proposed structures.