Quinazolines and 1,4-Benzodiazepines. LXI. (1) Syntheses of 7-Acetyl-1,4-benzodiazepines

Robert Y. Ning, Pradeep B. Madan and Leo H. Sternbach*

Chemical Research Department, Hoffmann-La Roche, Inc., Nutley, New Jersey 07110

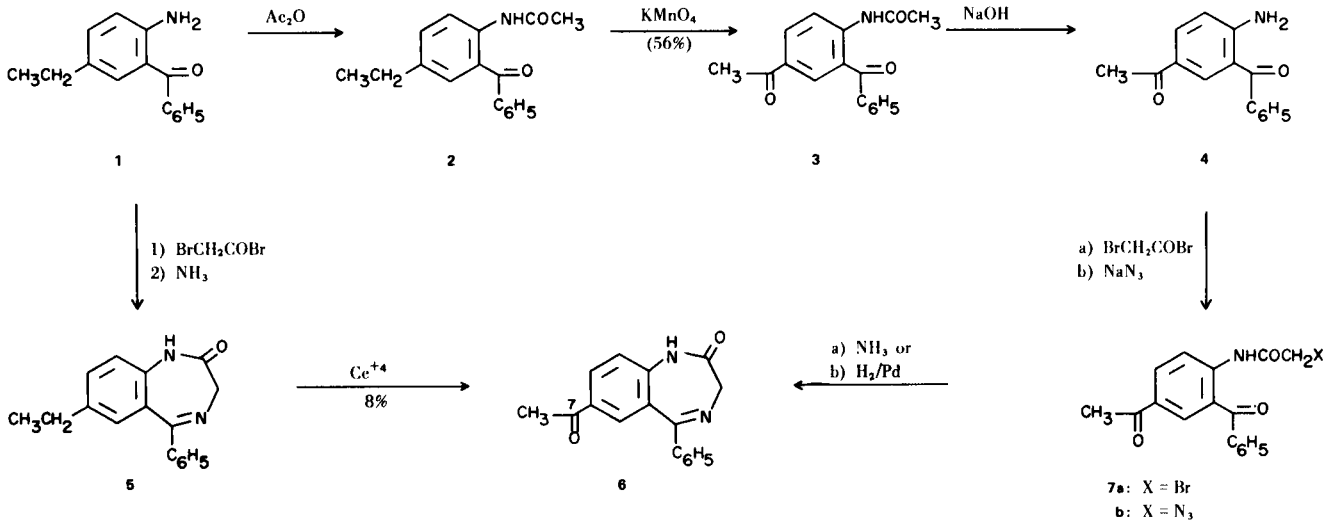
Received July 25, 1973

Methods for the synthesis of the biologically active 7-acetyl-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one (**6**) are described. This includes two new methods for the preparation of 5-acetyl-2-aminobenzophenone (**4**). The crucial steps in these syntheses involve, respectively, the oxidation of an ethyl group to an acetyl group with permanganate or ceric ions (**2** → **3**; **5** → **6**), the selective reaction of methyl lithium with the cyano group of 7-cyano-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one (**8**) and the efficient condensation of benzyl cyanide with the ethylene ketal of *p*-nitroacetophenone to form the anthranil **11**.

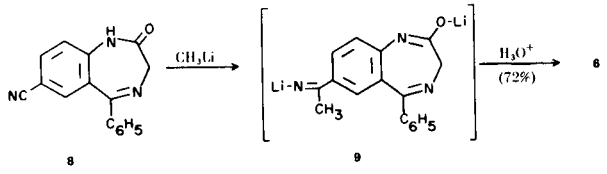
The nature of the substituent in the 7-position of 1,4-benzodiazepines is of crucial importance for the biological activities of these compounds (2,3). Although the substitution of the phenothiazine nucleus with acetyl, propionyl and butyryl groups has led to widely used medicinals (4), the introduction of alkanoyl groups into the 7-position of 1,4-benzodiazepines has not been accomplished until very recently. 7-Acetyl-1,4-benzodiazepines (5,6) were found to be highly active CNS agents. We wish to report here, three practical methods for the preparation of the 7-acetyl-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one (**6**) (7).

Schemes I, II and III depict three different reaction sequences leading to the 7-acetyl-1,4-benzodiazepin-2-one **6**. The crucial steps in Scheme I involve controlled oxidation of an ethyl group to an acetyl group (**2** → **3**; **5** → **6**). Starting with 2-amino-5-ethylbenzophenone **1**, obtained from *p*-ethylaniline in analogy to a published procedure (8), the acetanilide **2** and the 7-ethylbenzodiazepinone **5** (9) were prepared. Controlled oxidation of **2** with potassium permanganate (10) afforded the acetyl acetanilide **3** in 56% yield. The acetanilide **3** was readily converted to the aminoketone **4** and the bromoacetanilide **7a**. Due to the unsatisfactory yield (25%) encountered in the amination-cyclization sequence (**7a** → **6**), **7a** was converted to the azide **7b**, which on hydrogenation (11) and heating afforded **6** in 70% yield. Some difficulty was encountered in attempting to oxidize the ethylbenzodiazepinone **5** to **6**. Using ceric ammonium nitrate in aqueous acetic acid, however, a conversion in 8% yield was realized. Due to the availability of alternate routes, this yield was not optimized.

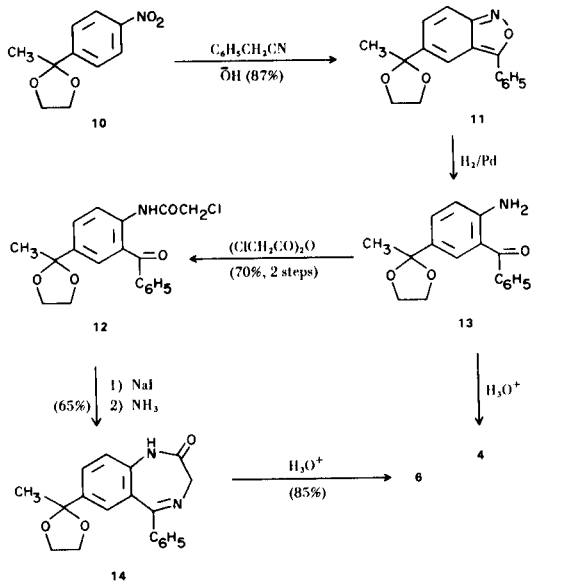
SCHEME I



SCHEME II



SCHEME III



The availability of 7-cyanobenzodiazepines (12) enabled us to study their reactions with organometallic reagents. Treatment of a tetrahydrofuran solution of 7-cyano-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one (**8**) with an excess of methyl lithium at Dry-ice temperature followed by the mild hydrolysis with dilute hydrochloric acid of the reaction mixture gave the desired acetylbenzodiazepinone **6** in 72% yield. The dianionic state of the intermediate **9** apparently preserved the normally sensitive diazepine ring from further reaction with methyl lithium.

The most satisfactory method for the synthesis of **6** is outlined in Scheme III. The condensation (13) of the readily available ethylene ketal of *p*-nitroacetophenone, **10**, (14) with phenylacetonitrile afforded the 2,1-benzisoxazole (anthranil) **11** in 87% yield. The ketal function remained intact during catalytic hydrogenation (15) (**11** → **13**), chloroacetylation (**13** → **12**) and amination (**12** → **14**) affording 1,3-dihydro-7-(2-methyl-1,3-dioxolan-2-yl)-5-phenyl-2*H*-1,4-benzodiazepin-2-one (**14**) in 40% overall yield from **11**. Mild hydrolysis of **14** yielded **6**.

These methods have permitted us to prepare a large number of biologically active 1,4-benzodiazepines containing formyl and other lower alkanoyl substituents in position 7 and derivatives thereof (16).

EXPERIMENTAL

All melting points were taken in capillaries heated in oil baths, and are corrected. Infrared spectra were determined on a Beckmann IR-9 or a Perkin-Elmer 621 grating spectrometer, mass spectra on a J[illegible]olco-01SG or a CEC-21-110 spectrometer, nuclear magnetic resonance spectra on a Varian A-60 or a Varian HA-100 spectrometer, using tetramethylsilane as internal standard and ultraviolet spectra with a Cary 14M or 15 recording spectrometer. Solvents used were of reagent grade purity. Petroleum ether used boils at 30-60°. Unless otherwise specified, all solvents were evaporated on a Büchi Rotavapor evaporator under water-aspirator pressure using a water bath set at 30-80°.

The progress of reactions was routinely followed by thin layer chromatography (tlc). The tlc was performed on glass plates coated with Mallinckrodt Silica 7GF5 (with fluorescent indicator) in the case of analytical tlc and Merck silica gel PF254 in the case of preparative tlc. All plates were activated by heating to 100° for 1 hour then stored at 20-50°. The chromatograms were developed over a distance of 10 cm then viewed or photographed under uv light.

2-Amino-5-ethylbenzophenone (**1**).

To a stirred solution of 41.7 g. (0.36 mole) of zinc chloride in 175 ml. (1.52 moles) of benzoyl chloride maintained at 140°, 29.1 g. (0.24 mole) of *p*-ethylaniline was added in portions. The mixture was heated under reflux at 210-220° for 1 hour. Much gaseous hydrogen chloride was expelled. The temperature was then lowered to 140°, and the excess benzoyl chloride was removed by distillation at water aspirator pressure. Without letting the mixture cool, 100 ml. of 6 *N* hydrochloric acid was added carefully at about 140° and the reaction mixture was stirred and heated under reflux at 140-160° for 20 hours. The mixture was partially cooled. Methylene chloride (about 300 ml.) was added, followed by about 300 ml. water. The mixture was stirred until all solids dissolved. The aqueous layer was extracted two more times with methylene chloride. The combined methylene chloride layers were washed thoroughly with 3 *N* hydrochloric acid, 3 *N* sodium hydroxide and water in this sequence. After drying over anhydrous sodium sulfate and evaporation of methylene chloride a dark gum was obtained. This gum contained predominently **1** by tlc. Due to difficulties encountered in the crystallization of **1** this crude product was utilized without purification.

In order to isolate **1** for characterization, the following purification was conducted:

The gum was chromatographed on a column of 500 g. of activity I alumina. Elution with 10% ether in benzene gave 38.0 g. (71%) of a gum (single spot on tlc). Crystallization from petroleum ether gave pale yellow plates, m.p. 54-56°; uv max (2-propanol): 240 nm (ϵ 24,200) and 402 (5760).

Anal. Calcd. for $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.22. Found: C, 79.66; H, 6.69; N, 6.08.

2'-Benzoyl-4'-ethylacetanilide (**2**).

To a solution of 90 g. (0.4 mole) of crude 2-amino-5-ethylbenzophenone in 400 ml. of benzene was added 84 ml. (91.0 g., 0.8 mole) of acetic anhydride and the reaction mixture was heated under reflux for 45 minutes.

On cooling the reaction mixture was concentrated to yield a semi-solid. Crystallization from ethanol afforded 56.0 g. (53%) of **2** as a pale brown powder, m.p. 109-110.5°. Repeated recrystallizations from ethanol gave colorless needles, m.p. 112-113.5°; ir (potassium bromide): 1670 and 1645 cm^{-1}.

Anal. Calcd. for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24.

Found: C, 76.26; H, 6.42; N, 5.46.

4'-Acetyl-2'-benzoylacetanilide (**3**).

A three-necked 3 l. flask was charged with 5.0 g. (125 mmoles) of magnesium oxide, 17.0 ml. (270 mmoles) of concentrated nitric acid and 2 l. of water. To this solution was added 13.3 g. (50 mmoles) of **2** and 19.5 g. (125 mmoles) of potassium permanganate. The reaction mixture was heated with stirring at 60° ± 2° for 5 hours.

The reaction mixture was chilled in ice. Manganese dioxide was dissolved by reduction with a stream of gaseous sulfur dioxide. The remaining pale yellow solid was collected and washed with water. After two recrystallizations from ethanol, 6.2 g. (56% based on unrecovered starting material) of **3** was obtained as colorless needles, m.p. 115-116°; ir (potassium bromide): 1700, 1680 and 1640 cm^{-1}. From the ethanolic mother liquors, 2.7 g. of starting material (**2**) was recovered.

Anal. Calcd. for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37; N, 4.98. Found: C, 72.30; H, 5.52; N, 4.96.

5-Acetyl-2-aminobenzophenone (**4**).

A) From **3**.

To a solution of 5.6 g. (20 mmoles) of **3** in 100 ml. of ethanol was added 100 ml. (0.2 mole) of 2 *N* sodium hydroxide. The mixture was heated under reflux for 3 hours. On cooling, pale yellow crystals precipitated. The crystals were collected and washed with ethanol. After recrystallization from benzene-petroleum ether, 3.5 g. (73%) of **4** was obtained as yellow prisms, m.p. 153-154.5°; ir (potassium bromide): 1675, 1660 and 1610 cm^{-1}; uv max (2-propanol): 242 nm (ϵ 20,220), 308 (18,900) and 371 (6100).

Anal. Calcd. for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.48; N, 5.86. Found: C, 75.47; H, 5.41; N, 5.65.

B) From Ketal **13**.

To a solution of 1.00 g. (3.54 mmoles) of 2-amino-5-(2-methyl-1,3-dioxolan-2-yl)benzophenone (**13**) in 30 ml. of ethanol, was added 14 ml. of 1 *M* perchloric acid. The mixture was stirred at room temperature ovemight. The ethanol insolubles were collected. The filtrate was basified with 3 *N* sodium hydroxide, partitioned between methylene chloride and water. The organic layer was dried, evaporated to dryness. The residue was combined with the ethanol insolubles and recrystallized from benzene-hexane to yield 450 mg. (54%) of yellow needle clusters, m.p. 152-154°. By mixture m.p. and thin layer chromatography this product was found identical to **4** prepared above.

1,3-Dihydro-7-ethyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one (**5**).

A mixture of 10.0 g. (41.6 mmoles) of 2-amino-5-ethylbenzophenone (**1**), 16.6 g. (83.2 mmoles) of bromoacetyl bromide, and 300 ml. of benzene was heated under reflux for 1 hour. On cooling the mixture was washed with ice-cold dilute alkali and water and dried. The solvent was removed to yield 10.0 g. of crude bromoacetanilide as a pale brown oil. The oil was dissolved in 200 ml. of methylene chloride and was added to 250 ml. of ammonia; the mixture was stirred under refluxing ammonia for 2 hours. The excess of ammonia was allowed to evaporate overnight. The insoluble inorganic salts were removed by filtration. The filtrate was concentrated to dryness, and the residue was dissolved in 300 ml. of ethanol, heated under reflux for 2 hours. On cooling, the ethanol solution was evaporated to dryness. The residue, on crystallization from benzene-petroleum ether, gave 5.00 g. (43%) of **5** as yellow prisms, m.p. 192-194°; ir (potassium bromide): 1675 cm^{-1} (amide); uv max (2-propanol): 229 nm (ϵ 36,750) and 314 (2450); nmr (deuteriochloroform): δ 1.17 (t, 3, CH_3), 2.57 (q, 2, CH_2), 4.32 (s, 2, CH_2), 7.1-7.6 (m, 8, aromatic) and 9.70 ppm (s, 1, NH).

An analytical sample was prepared by recrystallization from benzene-petroleum ether, m.p. 194-195°.

Anal. Calcd. for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10; N, 10.60. Found: C, 77.46; H, 6.22; N, 10.46.

7-Acetyl-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one (**6**).

A) From **7b**.

To a solution of 2.0 g. (6.2 mmoles) of azidoacetanilide **7b** in 125 ml. of tetrahydrofuran was added 350 mg. of 10% palladium-on-carbon and the mixture was hydrogenated at one atmosphere for 2 hours. The catalyst was removed by filtration through a pad of Celite. The solution was evaporated to dryness. The pale yellow solid obtained was dissolved in 125 ml. of ethanol and heated to a reflux for 2 hours. Evaporation of ethanol gave an oil, which crystallized from benzene-petroleum ether as pale yellow prisms. The yield was 1.2 g. (70%), m.p. 184-186.5°; ir (Nujol) 1680 cm^{-1} (broad), uv max (2-propanol): 221 nm (ϵ 24,000) and 252 (24,700); nmr (deuteriochloroform): δ 2.47 (s, 3, CH_3), 4.35 (s, 2, CH_2), 7.2-8.2 (m, 8, aromatic) and 10.28 ppm (s, 1, NH).

Anal. Calcd. for $C_{17}H_{14}N_2O_2$: C, 73.37; H, 5.07; N, 10.06. Found: C, 73.19; H, 5.36; N, 10.05.

B) From **7a**.

A solution of 2.4 g. (6.8 mmoles) of bromoacetanilide **7a** in 10 ml. of methylene chloride was added to 25 ml. of liquid ammonia at -78°, chilled in a Dry Ice-acetone bath. After stirring for 2 hours, the Dry-Ice bath was removed, and the liquid ammonia allowed to evaporate. The methylene chloride layer was washed with water, dried over anhydrous sodium sulfate, and evaporated to dryness. The oily residue was dissolved in 40 ml. of ethanol and heated to reflux for 1 hour. Evaporation of ethanol and repeated recrystallization of the residue from benzene-petroleum ether gave 470 mg. (25%) of **6** as a yellow powder, m.p. 158-160°. The tlc and infrared spectrum of this product are identical to that of the higher melting material obtained above *via* procedure A.

C) From 7-Ethyl Analog **5**.

A solution of 132 mg. (0.50 mmole) of **5** in 4 ml. of glacial acetic acid was mixed with a solution of 1.10 g. (2.0 mmoles) of ceric ammonium nitrate (from Matheson Coleman and Bell Co.) in 4 ml. of water. The mixture, a clear solution, was allowed to stand at room temperature. After 1 day, the mixture was diluted with 50 ml. of water and extracted twice with equal volumes of methylene chloride. The combined methylene chloride layers were washed twice with water, dried over anhydrous sodium sulfate and evaporated to dryness. The residual yellow gum was separated by preparative thin-layer chromatography (silica gel, Brinkmann, PF 254 2 mm thick, 2 plates measuring 20 cm x 20 cm; ether used as eluent). Pure **5** was isolated as a gum which crystallized from a small volume of acetonitrile as light yellow prisms (10.1 mg., 8%), m.p. 187-189°. Infrared spectrum of this compound is identical to **6** obtained above.

D) From 7-Cyano Analog **8**.

A solution of 1.30 g. (5.0 mmoles) of 7-cyano-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one (12) (**8**) in 200 ml. of dry tetrahydrofuran was chilled in a bed of powdered Dry-Ice under nitrogen. A 1.55 *M* solution of methyl lithium in ether (10.0 ml., 15 mmoles) was added in one portion. The mixture was stirred

under nitrogen for 0.5 hour at the Dry-Ice temperature, then decomposed by pouring with stirring into 500 ml. of 0.1 *N* hydrochloric acid. After 10 minutes at room temperature, the mirky solution was basified to about *p*H 8 with 1 *N* sodium hydroxide and the product isolated by extraction with methylene chloride. Crystallization from ether afforded 1.00 g. (72%) of **6**, m.p. 186-187°. Tlc and infrared spectrum of this material are identical to that obtained above.

E) From the Ketal **14**.

A solution of 100 g. (0.31 mole) of 1,3-dihydro-7-(2-methyl-1,3-dioxolan-2-yl)-5-phenyl-2*H*-1,4-benzodiazepin-2-one (**14**) in 750 ml. of 1 *N* hydrochloric acid was stirred at room temperature for 0.5 hour. The mixture was chilled in an ice bath and neutralized (*p*H about 4) with 10 *M* potassium hydroxide. Product was extracted with methylene chloride. On crystallization from ether, 73.2 g. (85%) of colorless prisms were obtained, m.p. 191-193°. Tlc and infrared spectrum of this material are identical to **6** obtained above.

4'-Acetyl-2'-benzoyl-2-bromoacetanilide (**7a**).

To a solution of 7.2 g. (30 mmoles) of 2-amino-5-acetylbenzophenone in 100 ml. of benzene was added 12.06 g. (60 mmoles) of bromoacetyl bromide. The mixture was heated under reflux for 3 hours. On cooling, the reaction mixture was washed with ice-cold dilute alkali, and water, dried over anhydrous sodium sulfate and evaporated to yield a buff colored solid. On recrystallization from benzene-petroleum ether 7.8 g. (72%) of **7a** was obtained as a buff colored amorphous solid, m.p. 118-120°. A portion of this material (1.7 g.) on further recrystallization yielded red hexagonal prisms (1.0 g.), m.p. 124.5-125.5°.

Anal. Calcd. for $C_{17}H_{14}BrNO_3$: C, 56.70; H, 3.92; N, 3.89. Found: C, 57.07; H, 3.91; N, 3.84.

4'-Acetyl-2-azido-2'-benzoylacetanilide (**7b**).

To a solution of 3.0 g. (8.4 mmoles) of **7a** (m.p. 118-120°) in 120 ml. of methanol, was added 1.08 g. (16.8 mmoles) of sodium azide in one portion. The reaction mixture was heated on a steam bath for 15 minutes. On cooling, **7b** precipitated as pale pink microprisms. Upon recrystallization from ethanol, 2.0 g. (75%) of pink microprisms were obtained, m.p. 144-145°; ir (potassium bromide): 2130 cm^{-1} (N_3).

Anal. Calcd. for $C_{17}H_{14}N_4O_3$: C, 63.35; H, 4.38; N, 17.38. Found: C, 63.40; H, 4.22; N, 17.17.

5-(2-Methyl-1,3-dioxolan-2-yl)-3-phenyl-2,1-benzisoxazole (**11**).

To a room temperature solution of 100 g. (2.5 moles) of sodium hydroxide in 500 ml. of methanol was added 58.6 g. (0.50 mole) of phenylacetonitrile followed by 104.0 g. (0.50 mole) of 2-methyl-2-(4-nitrophenyl)-1,3-dioxolane (**10**) (14). The reaction temperature rose to about 55° in the first 0.5 hour of stirring. After 16 hours of vigorous stirring, the light yellow amorphous solid that precipitated was collected on a filter, and was washed thoroughly with water and small portions of cold methanol. The light yellow powder weighed 122 g. (87%), m.p. 137-138°. Analytical sample prepared from recrystallizations with methanol were light yellow plates, m.p. 137-138°; uv max (2-propanol): 247 nm (ϵ 15,150), 254 (16,220) and 344 (15,620).

Anal. Calcd. for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37; N, 4.98. Found: C, 72.35; H, 5.49; N, 4.96.

2'-Benzoyl-2-chloro-4'-(2-methyl-1,3-dioxolan-2-yl)acetanilide (**12**).

A solution of 116.3 g. (0.4 mole) of crude 2-amino-5-(2-methyl-1,3-dioxolan-2-yl)benzophenone, 106.0 g. (0.62 mole) of chloroacetic anhydride in 850 ml. of benzene was kept in a refrigerator at about 5° overnight. The mixture was washed with 500 ml. of cold aqueous 3 *N* sodium hydroxide, and water then dried over anhydrous sodium sulfate. The benzene solution was evaporated to dryness. The residue on crystallization from ethanol gave, in two crops, 104.3 g. (70%, over two steps from benzisoxazole **11**) of colorless needles, m.p. 131-133°, ir (potassium bromide): 1680 and 1640 cm^{-1}.

Anal. Calcd. for $C_{19}H_{18}ClNO_4$: C, 63.43; H, 5.04; N, 3.89. Found: C, 63.73; H, 5.01; N, 3.87.

2-Amino-5-(2-methyl-1,3-dioxolan-2-yl)benzophenone (**13**).

A solution of 113.7 g. (0.40 mole) of 5-(2-methyl-1,3-dioxolan-2-yl)-3-phenyl-2,1-benzisoxazole (**11**), 1000 ml. of tetrahydrofuran and 20 ml. of triethylamine was hydrogenated at room temperature and 1 atmosphere until 1 mole equivalent of hydrogen was absorbed (about 2 hours). The catalyst was removed by filtration over a pad of Celite. The filtrate was evaporated to dryness to yield 116.3 g. of a yellow amorphous solid, m.p. 96-99°. This crude **13** was used without further purification in the next step. Purification may be carried out by chromatography on neutral alumina (Woelm activity I). Elution with 20% ether in methylene chloride, and crystallization from methylene chloride-hexane gave yellow prisms m.p. 112-114°, ir (potassium bromide): 1620 cm^{-1}.

Anal. Calcd. for $C_{17}H_{17}NO_3$: C, 72.06; H, 6.05; N, 4.94. Found: C, 71.88; H, 6.13; N, 4.90.

1,3-Dihydro-7-(2-methyl-1,3-dioxolan-2-yl)-5-phenyl-2*H*-1,4-benzodiazepin-2-one (**14**).

A 5 liter three-necked round bottom flask equipped with a stirrer and a reflux condenser was charged with 48.0 g. (0.133 mole) of 2'-benzoyl-2-chloro-4'-(2-methyl-1,3-dioxolan-2-yl)acetanilide (**12**), 39.9 g. (0.266 mole) of sodium iodide and 2500 ml. of acetone. The mixture was heated under reflux for 0.5 hour. On cooling the inorganic solids were removed by filtration. The filtrate was evaporated to dryness. The residue was dissolved in 2000 ml. of tetrahydrofuran and added to a 5 liter three-necked flask equipped with a stirrer and Dry-Ice condenser charged with 1500 ml. of ammonia. The mixture was stirred under refluxing ammonia for 5 hours. The excess ammonia was allowed to evaporate overnight. The insoluble inorganic salts were removed by filtration. The filtrate was evaporated to dryness. The residue was partitioned between methylene chloride and water. The methylene chloride layer was washed with water, dried over anhydrous sodium sulfate, and evaporated to dryness. The residue on crystallization from ethanol, gave, in two crops, 31.7 g. (74%) of colorless prisms, m.p. 248-250°. After recrystallization by solution in 150 ml. of dimethylformamide at 100° and addition of an equal volume of ethanol followed by chilling, the yield was 28.0 g. (65%) m.p. 249-251°, ir (potassium bromide): 1670 cm^{-1}; nmr (deuteriochloroform): δ 1.58 (s, 3, CH_3), 3.5-4.1 (m, 4, OCH_2CH_2), 4.29 (s, 2, CH_2), 7.1-7.7 (m, 8, aromatic) and 9.65 ppm (s, 1, NH).

Anal. Calcd. for $C_{19}H_{18}N_2O_3$: C, 70.79; H, 5.63; N, 8.69. Found: C, 70.81; H, 5.80; N, 8.63.

Acknowledgement.

We thank Dr. R. P. W. Scott and his staff in our Physical Chemistry Department, in particular, Dr. W. Benz for mass spectra, Dr. F. Scheidl for elemental analyses, Dr. V. Toome for uv measurements, Mr. S. Traiman for ir spectra and Dr. T. Williams

for nmr spectra. We are grateful to Mrs. B. Sluboski for technical assistance.

REFERENCES

(1) Paper LX. R. Jaunin and W. Arnold, *Helv. Chim. Acta*, 56, 2569 (1973).

(2) L. H. Sternbach, L. O. Randall, R. Banziger and H. Lehr in "Drugs Affecting the Central Nervous System," Vol. 2, A. Burger, Ed., Marcel Dekker, New York, N. Y., 1968, p. 237.

(3) L. O. Randall, W. Schallek, L. H. Sternbach and R. Y. Ning in "Psychopharmacological Agents," Vol. III, M. Gordon, Ed., Academic Press, New York, N. Y., in press.

(4) M. Gordon in "Psychopharmacological Agents," Vol. II, M. Gordon, Ed., Academic Press, New York, N. Y., 1967, Chapter 1.

(5) P. A. Wehrli, R. I. Fryer and L. H. Sternbach, U. S. Patent 3,553,206 (1971); *Chem. Abstr.*, 75, 5974d (1971).

(6) Grindstedvaerket A. S., Belgian Patent 778191 (1972).

(7) After this work was complete, the synthesis of compound **6** appeared in reference 6.

(8) L. H. Sternbach, R. Ian Fryer, W. Metlesics, G. Sach and A. Stemple, *J. Org. Chem.*, 27, 3781 (1962).

(9) According to the method of L. H. Sternbach, R. Ian Fryer, W. Metlesics, E. Reeder, G. Sach, G. Saucy and A. Stempel, *J. Org. Chem.*, 27, 3788 (1962).

(10) J. R. Holsten and E. H. Pitts, Jr., *ibid.*, 26, 4151 (1961).

(11) J. B. Petersen and K. H. Lakowitz, *Acta Chem. Scand.*, 23, 971 (1969).

(12) L. H. Sternbach, G. Saucy, F. A. Smith, M. Müller and J. Lee, *Helv. Chim. Acta.*, 46, 1720 (1963).

(13) R. B. Davis and L. C. Pizzini, *J. Org. Chem.*, 25, 1884 (1960).

(14) O. Gisvold and H. V. Maulding, Jr., *J. Pharm. Sci.*, 57, 784 (1968).

(15) G. N. Walker, *J. Org. Chem.*, 27, 1929 (1962).

(16) See for instance R. Y. Ning and L. H. Sternbach, U. S. Patents 3,627,754 (1971); 3,682,892 and 3,686,308 (1972).