of 1-bromoisoquinoline (0.05 mole), in 50 ml. of absolute ether, was run into a solution on *n*-butyllithium, prepared from 8.4 g. of butyl bromide and 0.87 g. of lithium in 100 ml. ether, at −60° bath temperature. After the addition, the mixture was stirred for 0.5 hr. at −60° and then a solution of 14 g. of 1,1′-diisoquinolyl ketone (IV, 0.05 mole) in 150 ml. of absolute pyridine was added gradually at −60°. (The ketone precipitated after dissolving in hot pyridine in fine crystals. The rest of the suspension was therefore rinsed out of the dropping funnel with more pyridine into the reaction flask.) The mixture was stirred vigorously at −60° for 2 hr., then it was allowed to warm up to room temperature and was stirred for another 5 hr.

The dirty green mixture was acidified with aqueous sulfuric acid. The insoluble material was filtered and dissolved in 18*N* sulfuric acid. The acid solutions were combined and neutralized. The precipitate was washed with petroleum and then boiled with alcohol. The extract yielded 2.60 g. of the original ketone, including the recoveries from the mother liquor. The alcohol insoluble part was boiled with 300 ml. of butanol, whereupon 1.35 g. of VI was obtained from the solution; the mother liquor yielded 2.05 g. of IV. The solid residue of the butanol was taken up in 300 ml. of butanol again and dissolved by refluxing. An additional 2.85 g. of VI was obtained on cooling the solution and working up the mother liquor. Recovery of the ketone was 4.65 g., 33%. Total yield of carbinol 4.20 g., 20%, m.p. 244–245°.

Anal. Calcd. for $C_{28}H_{19}ON_3$: C, 81.26; H, 4.74; N, 10.02. Found: C, 81.34; H, 4.63; N, 10.16.

Reduction with zinc amalgam. A solution of 250 mg. of the carbinol in 15 ml. of 4*N* hydrochloric acid was reluxed for 1 hr. with amalgamated zinc turnings. A red solution was obtained which precipitated a brownish matter on neutralizing with ammonia. The product was taken up in chloroform, the solution dried and concentrated. On standing, crystals appeared; the amount was increased on adding carbon tetrachloride. Recrystallization from carbon tetrachloride-petroleum ether (b.p. 100–115°) gave crystals, m.p. 212°. On mixing with an authentic sample of 1-hydroxyisoquinoline no depression of the melting point was observed. The ultraviolet spectrum was identical with that of the hydroxyisoquinoline.

Acknowledgment. We wish to thank Dr. R. E. Lundin from the U. S. Department of Agriculture, 800 Buchanan Street, Albany, Calif., for the investigation and explanation of the NMR spectra.

DAVIS, CALIF.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES, HOFFMANN-LA ROCHE INC.]

Quinazolines and 1,4-Benzodiazepines. IV.[1,2] Transformations of 7-Chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine 4-Oxide[3]

L. H. STERNBACH AND E. REEDER

Received June 19, 1961

7-Chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine 4-oxide (I) and its acetyl derivative (II) can be hydrolyzed to 7-chloro-5-phenyl-3H-1,4-benzodiazepin-2(1H)-one 4-oxide (III). Other methods are described for the synthesis of this compound and its conversion into pharmacologically active benzodiazepinones.

The interesting finding that 7-chloro-2-methylamino-5-phenyl-3H,1,4-benzodiazepine 4-oxide (I)[4] hydrochloride and its acetyl derivative, 7-chloro-2-(*N*-methyl-acetamido)-5-phenyl-3H-1,4-benzodiazepine 4-oxide (II), showed very similar muscle relaxant, sedative, and anticonvulsant properties in animals suggested that these two compounds owed their activity to a common degradation product.

In the search for such a product the decomposition of II was studied. Treatment with alkali resulted in its reconversion into I[5]; however, hydrolysis with dilute mineral acid at room temperature gave an almost quantitative yield of a degradation product (III)[6] which was pharmacologically[4] very similar to the starting material. The same compound was also formed on prolonged standing of an aqueous solution of the hydrochloride of 7-chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine 4-oxide.[7]

The composition and genesis indicated for this degradation product the structure III. This was confirmed by the infrared spectrum (0.3% solution in chloroform) showing a strong carbonyl band at 1706 cm.$^{-1}$, and an NH hydrogen band at 3400 cm.$^{-1}$

Additional evidence was supplied by the chemical behavior of the compound. It had acidic properties which can be attributed to the electron withdrawing properties of the *N*-oxide oxygen. It was soluble in 1*N* alkali and recovered unchanged on acidification. On prolonged treatment with an excess of alkali the amide linkage was split and an amino acid (VIII) was formed which could be reconverted into the lactam III by heating or prolonged treatment with

(1) Paper III of this series, L. H. Sternbach, E. Reeder, O. Keller, W. Metlesics, *J. Org. Chem.*, **26**, 4488 (1961).

(2) Presented in part at the Gordon Research Conference, Medicinal Chemistry Section, August 1961.

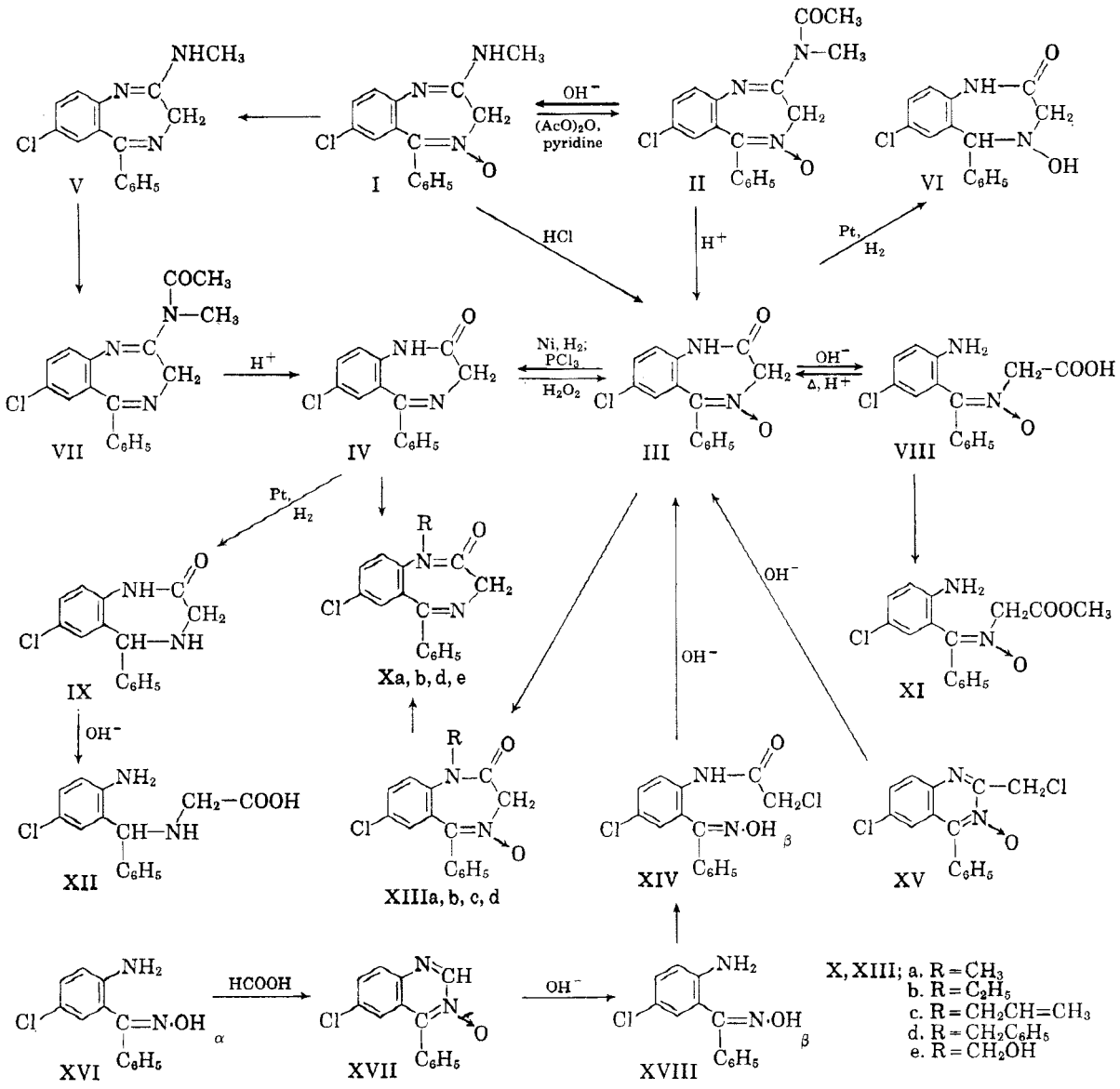
(3) Marketed under the trade name Librium®.

(4) The pharmacological investigations were done by Dr. L. O. Randall and his co-workers and will be published elsewhere.

(5) Paper II of this series, L. H. Sternbach and E. Reeder, *J. Org. Chem.*, **26**, 1111 (1961).

(6) In addition *N*-methylacetamide was formed, which proved the position of the acetyl group on the exocyclic nitrogen atom.

(7) B. A. Koechlin and M. A. Schwartz (Federation Proceedings Vol. 20, Part 1, 171, March 1961) later found this degradation product (III) also in the blood and urine of Librium® treated people and animals. It has, however, not yet been established whether the biological activity of Librium® is due to conversion into this compound.



mineral acid. The acid (VIII) was characterized by its methyl ester XI and the acetyl derivative of the ester.

Treatment of the lactam III with phosphorus trichloride or hydrogenation with Raney nickel as catalyst removed the *N*-oxide oxygen and gave an almost quantitative yield of the corresponding "desoxylactam"[8] IV which in turn could be re-oxidized with hydrogen peroxide to compound III. This "desoxylactam" IV could also be obtained in good yield by mild acid hydrolysis of the acetyl derivative VII which was prepared in the conventional way from the "desoxy" derivative V.[5]

The lactam III was also synthesized by other methods. The chloromethylquinazoline 3-oxide (XV)[9] on treatment with one mole of alkali underwent ring enlargement[10] and gave III in good yield Another method was the alkali treatment of the chloroacetyl derivative of 2-amino-5-chlorobenzophenone β-oxime which caused an intramolecular "*N*-alkylation" and the formation of the "lactam" III. The β-oxime was prepared in larger quantities by transforming the α-oxime XVI first into the quinazoline XVII by refluxing with formic acid and then saponifying XVII to the β-oxime by treatment with alkali.[11] The chloroacetylation to XIV was done by a Schotten-Baumann reaction.

Both the lactam III and the desoxylactam IV

(8) Compounds lacking the *N*-oxide grouping shall be called "desoxy" derivatives.

(9) Paper I of this series, L. H. Sternbach, S. Kaiser, and E. Reeder, *J. Am. Chem. Soc.*, **82**, 475 (1960).

(10) This ring enlargement is analogous to the reaction occurring on treatment of XV with methylamine.[5]

(11) K. v. Auwers and O. Jordan (*Ber.*, **57**, 800 (1924)) first described the conversion of the *o*-aminobenzophenone α-oxime into the β-isomer by this method. They assumed that the treatment with formic acid converted the oxime into a formyl derivative. In our case the quinazoline 3-oxide XVII was formed as was proven by analysis and infrared spectrum.

could be hydrogenated in the presence of a platinum catalyst. The "lactam" formed the hydroxylamine derivative VI; the "desoxylactam" yielded the dihydrodesoxy derivative IX, which could be hydrolyzed to the formerly described[5] amino acid XII.

The lactam III could be substituted in position 1 as described in the Experimental part and was thus transformed into compounds XIIIa,b,c, and d.[12] These in turn on treatment with phosphorus trichloride or hydrogenation with Raney nickel catalyst yielded the corresponding "desoxy" derivatives Xa, b, and d. These compounds could also be prepared by substituting the desoxylactam IV in position 1. The hydroxymethyl derivative Xe was obtained from IV by treatment with paraformaldehyde.

All benzodiazepines showed interesting pharmacological properties.[4] The methyl-"desoxylactam" Xa[13] was particularly active as a muscle relaxant, sedative and anticonvulsant.

EXPERIMENTAL

All melting points are corrected. The infrared and ultraviolet absorption spectra of starting materials and reaction products were compared wherever necessary in order to establish structural changes. The infrared spectra were determined in 0.3–3% chloroform solutions using a Perkin Elmer Model 21 spectrophotometer, the ultraviolet absorption spectra in isopropyl alcohol and in 0.1*N* hydrochloric acid.

7-Chloro-5-phenyl-3H-1,4-benzodiazepin-2(1H)-one 4-oxide (III). *A. From 7-chloro-2-(N-methylacetamido)-5-phenyl-3H-1,4-benzodiazepine 4-oxide* (II).[5] To a solution of 85.4 g. (0.25 mole) of II in 1250 cc. of dioxane was added at room temperature 250 cc. of 1*N* hydrochloric acid. The mixture was left at room temperature for 14 hr., diluted with ice water, made alkaline and extracted with ether to remove impurities. (The reaction product III remained in the alkaline solution.) The aqueous part was then neutralized with acetic acid and extracted with methylene chloride. The methylene chloride solution was dried, concentrated to a smaller volume, and the crystalline reaction product was precipitated by the addition of petroleum ether (b.p. 30–60°). The yield was 63.5 g. (89%). The pure material formed plates (from alcohol) melting at 235–236° dec. It is soluble in alkali and forms crystalline alkali metal salts.

Anal. Calcd. for $C_{16}H_{11}O_2N_3Cl$: C, 62.83; H, 3.86; N, 9.77. Found: C, 63.06; H, 3.92; N, 9.64.

In another experiment compound II was treated in the same way as described above with hydrochloric acid. Most of the dioxane was then removed by concentration *in vacuo*. The precipitated lactam III was filtered off and the aqueous solution extracted with some methylene chloride to remove the last traces of this product. The aqueous part was then neutralized with sodium hydroxide (no methylamine was present, as indicated by the absence of methylamine odor) and concentrated *in vacuo*. The residue was repeatedly extracted with boiling ether. The ether solutions were dried with sodium sulfate and concentrated *in vacuo*. The residual oil solidified. This product was *N*-methylacetamide, as proven by boiling point and identity of its infrared spectrum with the spectrum of an authentic sample. The yield was about 50%.

B. From 7-chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine 4-oxide (I) *hydrochloride.* A solution of 20 g. of the hydrochloride of I in 200 cc. of water was kept at room temperature for 30 days. The turbid mixture was then extracted repeatedly with benzene. The benzene solution was concentrated *in vacuo* and yielded 6 g. of an oil which on crystallization gave 1.2 g. of 7-chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine 4-oxide (I) and 1 g. of 7-chloro-5-phenyl-3H-1,4-benzodiazepin-2(1H)-one 4-oxide (III).

C. From 6-chloro-2-chloromethyl-4-phenylquinazoline 3-oxide hydrochloride.[9] To a suspension of 10.2 g. (30 mmoles) of the hydrochloride of XV in 150 cc. of dioxane, 60 cc. of 1*N* sodium hydroxide was added. The mixture was left at room temperature for 14 hr., concentrated *in vacuo* to a small volume, diluted with ice cold 3*N* alkali, and extracted with methylene chloride. The methylene chloride solution was discarded. The alkaline solution containing the reaction product was acidified with hydrochloric acid and extracted with methylene chloride. The methylene chloride solution was dried, concentrated *in vacuo*, and the residue crystallized. Thus 4.6 g. (53%) of III was obtained. In other experiments, the 6-chloro-2-chloromethyl-4-phenylquinazoline 3-oxide was used instead of the hydrochloride, and in that case only 1 mole of alkali was needed.

D. From 2-chloroacetamido-5-chlorobenzophenone β-oxime (XIV). To a solution of 6.4 g. (20 mmoles) of XIV in 60 cc. of dioxane was added 20 cc. of 1*N* sodium hydroxide. After 15 hr. the mixture was diluted with ice cold 1*N* sodium hydroxide and extracted with ether. The ether extract was discarded, the alkaline solution acidified and extracted with methylene chloride. The methylene chloride solution was concentrated to a small volume and diluted with petroleum ether, yielding 3.1 g. (54%) of III.

E. From 7-chloro-5-phenyl-3H-1,4-benzodiazepin-2(1H)-one (IV). A solution of 2.7 g. (10 mmoles) of IV and 1.2 cc. of a 30% solution of hydrogen peroxide (10 mmoles) in 15 cc. of glacial acetic acid was heated to 80°. Three additional portions of 0.6 cc. of 30% hydrogen peroxide each were introduced at 2-hr. intervals and the heating was continued for a total of 10 hr. After standing for 36 hr. at room temperature, the solution was diluted with water and ice, neutralized with aqueous potassium carbonate, and extracted with methylene chloride. The methylene chloride solution was extracted with 3*N* hydrochloric acid (160 cc.) in several portions in order to remove unchanged starting material IV. The organic layer was then dried, concentrated *in vacuo*, and the residue crystallized from methylene chloride, ether and petroleum ether to yield 0.55 g. (19%) of III.

Conversion of 2-amino-5-chlorobenzophenone α-oxime (XVI) *into the β-oxime* (XVIII).[11] A solution of 20 g. of 2-amino-5-chlorobenzophenone α-oxime (XVI) in 150 cc. of formic acid (98–100%) was refluxed for 3 hr., concentrated *in vacuo* to a small volume and neutralized with cooling with 3*N* sodium hydroxide. The precipitated quinazoline 3-oxide XVII was filtered and a small part was recrystallized for analysis from a mixture of methylene chloride and ether. It formed yellowish needles melting at 221–222.5°.

Anal. Calcd. for $C_{16}H_9N_3OCl$: C, 65.51; H, 3.53. Found: C, 65.12; H, 3.44.

The rest of the crude material was dissolved in 100 cc. of alcohol and, after the addition of 40 cc. of 3*N* sodium hydroxide, refluxed for 15 min. The solution was then partly concentrated *in vacuo*, diluted with water, and the β-oxime precipitated by the addition of Dry Ice. It was extracted with ether and crystallized by partial concentration. It formed prisms (7.7 g.) melting at 129–132° and was found to be identical with the formerly described β-oxime.[9]

2-Chloroacetamido-5-chlorobenzophenone β-oxime (XIV). Into a stirred, cooled (10–15°) solution of 26.2 g. (0.1 mole) of 2-amino-5-chlorobenzophenone β-oxime (XVIII) in 150 cc. of dioxane were introduced in small portions 12.4 g. (0.11 mole) of chloroacetyl chloride and an equivalent

(12) The strong band at 1700 cm. in the infrared spectrum indicates the presence of the unchanged carbonyl group.

(13) This product has the trade mark Valium.®

amount of 3*N* sodium hydroxide. The chloroacetyl chloride and sodium hydroxide solution were introduced alternately at such a rate as to keep the temperature below 15° and the mixture neutral or slightly alkaline. The reaction was completed after 30 min. The mixture was then acidified with hydrochloric acid, diluted with water and extracted with ether. The ether extract was dried and concentrated *in vacuo*. Upon the addition of ether to the oily residue, the product crystallized in colorless prisms melting at 166–167°. The yield was about 50%. The product gave a melting point depression with the compound derived from the α-oxime (m.p. 165–167°).[9]

Anal. Calcd. for $C_{15}H_{12}N_2O_2Cl_2$: C, 55.74; H, 3.74. Found: C, 56.01; H, 3.80.

7-Chloro-5-phenyl-3H-1,4-benzodiazepin-2(1H)-one (IV). *A. From 7-chloro-5-phenyl-3H-1,4-benzodiazepin-2(1H)-one 4-oxide* (III). A solution of 14.3 g. of III in 300 cc. of dioxane was hydrogenated in the presence of 20 g. of Raney nickel at atmospheric pressure and room temperature. The hydrogenation was stopped after the absorption of 1 mole of hydrogen. The reaction mixture was filtered, concentrated *in vacuo* to a small volume, and diluted with ether and petroleum ether. The precipitated crystals (12 g., 92% yield) formed, after recrystallization from acetone, colorless plate melting at 216–217°.

Anal. Calcd. for $C_{15}H_{11}ON_2Cl$: C, 66.65; H, 4.10; N, 10.35; Cl, 13.10. Found: C, 66.88; H, 3.90; N, 10.26; Cl, 13.11.

B. A solution of 15 g. of III and 25 cc. of phosphorus trichloride in 700 cc. of chloroform was refluxed for 30 min. The solution was then poured on ice, the mixture made alkaline with 50% sodium hydroxide and the organic layer was separated. The aqueous layer was extracted repeatedly with methylene chloride. The organic layers were combined, dried, filtered over a filter aid to remove a fine amorphous impurity, and concentrated *in vacuo* to dryness. The residue was crystallized from acetone and yielded 11.7 g. of IV.

C. From 7-chloro-2-(N-methylacetamido)-5-phenyl-3H-1,4-benzodiazepine (VII). To a solution of 3.2 g. of VII in 50 cc. of dioxane was added at room temperature 10 cc. of 1*N* hydrochloric acid. After 15 hr., 0.5 g. of precipitated starting material was filtered. The solution was diluted with water and extracted with methylene chloride. The methylene chloride solution was dried, concentrated *in vacuo* and the residue crystallized by the addition of acetone to yield 1.3 g. of crystalline IV.

7-Chloro-2-(N-methylacetamido)-5-phenyl-3H-1,4-benzodiazepine (VII). Two grams of 7-chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine[5] was dissolved with slight heating in a mixture of 10 cc. of acetic anhydride and 20 cc. of pyridine. The solution was left at room temperature for 16 hr., concentrated *in vacuo*, and the residue crystallized from a mixture of ether and petroleum ether. The product formed large colorless prisms melting at 162°. The yield was almost quantitative.

Anal. Calcd. for $C_{18}H_{16}N_3OCl$: C, 66.36; H, 4.95. Found: C, 66.35; H, 4.79.

N-(2-Amino-5-chlorobenzhydrylidene) glycine N-oxide (VIII). A solution of 50 g. (0.175 mole) of 7-chloro-5-phenyl-3H-1,4-benzodiazepin-2(1H)-one 4-oxide (III) in 375 cc. of 3*N* potassium hydroxide was stirred at room temperature for 24 hr. and the precipitated crude potassium salt of VIII was filtered. The yield was 58 g. (97%). The crude salt softened at 132° and melted at about 163° dec. This salt was converted into the free acid as described below:

An aqueous solution of 6.8 g. (0.02 mole) of the potassium salt was neutralized with 20 cc. of 1*N* hydrochloric acid. The precipitated acid was filtered and recrystallized from a mixture of methanol, ether, and petroleum ether. The product formed yellow needles (2.1 g., 34%) melting at 148–149° dec.; on further heating the product resolidified partly at about 158° and melted at about 200°.

Anal. Calcd. for $C_{15}H_{13}N_2O_3Cl$: C, 59.12; H, 4.30. Found: C, 58.80; H, 4.20.

The product could be easily reconverted into 7-chloro-5-phenyl-3H-1,4-benzodiazepin-2(1H)-one 4-oxide III. Refluxing a 0.3% benzene solution of VIII for 4 hr. yielded 64% of III. A 1.0% solution of VIII in 3*N* hydrochloric acid was kept at room temperature for 72 hr. and deposited 53% of 7-chloro-5-phenyl-3H-1,4-benzodiazepin-2(1H)-one-4-oxide (III).

Methyl ester. To a suspension of 3.3 g. of *N*-(2-amino-5-chlorobenzhydrylidene) glycine *N*-oxide (VIII) in about 50 cc. of methanol was added an excess of an ether solution of diazomethane. After a few minutes the reaction mixture was filtered and the filtrate concentrated *in vacuo* to dryness. The residue was crystallized from ether and yielded 1.3 g. (39%) of the crude methyl ester. The pure compound formed, after crystallization from a mixture of methanol, ether, and petroleum ether, yellow prisms melting at 155–156°.

Anal. Calcd. for $C_{16}H_{15}N_2O_3Cl$: C, 60.28; H, 4.74; MeO, 9.74. Found: C, 60.04; H, 4.46; MeO, 9.76.

Acetyl derivative of methyl ester. To a cooled solution of 1 g. of *N*-(2-amino-5-chlorobenzhydrylidene) glycine methyl ester *N*-oxide (XI) in 10 cc. of pyridine was added 3 cc. of acetic anhydride. The precipitated acetylation product (0.7 g.) was filtered after about 30 min. On recrystallization from methylene chloride it formed rhombic colorless plates melting at 208–209°.

Anal. Calcd. for $C_{18}H_{17}ClN_2P_4$: C, 59.92; H, 4.75. Found: C, 60.00; H, 4.64.

7-Chloro-4,5-dihydro-4-hydroxy-5-phenyl-3H-1,4-benzodiazepin-2(1H)-one (VI). 7-Chloro-5-phenyl-3H-1,4-benzodiazepin-2(1H)-one 4-oxide (III) (7.6 g.) was dissolved in 150 cc. of glacial acetic acid and hydrogenated in the presence of 0.6 g. of platinum oxide at room temperature and atmospheric pressure. The hydrogen uptake slowed down considerably after 6 hr., after the absorption of about 1.5 moles of hydrogen.[14] The hydrogenation was then interrupted, the reaction mixture heated, diluted with more glacial acetic acid to dissolve the precipitated hydrogenation product, and filtered. The filtrate was concentrated *in vacuo* to a small volume and the crystalline reaction product (4.6 g., 60% yield) was filtered. After recrystallization from acetic acid, the product formed colorless needles melting at 215–216°. It gave a melting point depression with the starting material.

Anal. Calcd. for $C_{15}H_{13}N_2O_2Cl$: C, 62.40; H, 4.53. Found: C, 62.07; H, 4.57.

7-Chloro-4,5-dihydro-5-phenyl-3H-1,4-benzodiazepin-2(1H)-one (IX). 7-Chloro-5-phenyl-3H-1,4-benzodiazepin-2(1H)-one (IV) (10.8 g.) was dissolved in 120 cc. of glacial acetic acid and hydrogenated in the presence of 1.2 g. of platinum oxide at room temperature and atmospheric pressure. The hydrogen uptake stopped after the absorption of 1 mole (1 hr.). The mixture was filtered, the solution concentrated *in vacuo* and the residue crystallized from dilute dimethylformamide. The yield was 9.55 g. (87.5%). The pure product melted at 184.5–185.5°.

Anal. Calcd. for $C_{15}H_{13}N_2OCl$: C, 66.06; H, 4.80; Found: C, 65.87; H, 4.80.

2-Amino-5-chloro-benzhydrylaminoacetic acid (XII). A mixture of 19 g. (0.07 mole) of 7-chloro-4,5-dihydro-5-phenyl-3H-1,4-benzodiazepin-2(1H)-one (IX), 200 cc. of a saturated (*ca.* 0.9*N*) methanolic solution of barium hydroxide, and 70 cc. of water was refluxed with stirring for 17 hr. The precipitated barium salt (23.5 g.) of XII was filtered, dissolved in 250 cc. of dimethylformamide, and freed from barium ions by the addition of 65.6 cc. of 1*N* sulfuric acid. The filtered solution was concentrated *in vacuo* to dryness and the residue crystallized from methanol yielding 16.4 g. (80%) of 2-amino-5-chloro-benzhydrylamino acetic acid softening at 191° and melting at 212–214°. The product was identical with the formerly described amino acid.[5]

Methyl ester. To a suspension of 5 g. of the acid in a small amount of ether was added an excess of an ether solution of

(14) The reaction product could not be easily purified if the hydrogenation were stopped after the uptake of the calculated 1 mole of hydrogen.

diazomethane. After complete solution, the reaction mixture was concentrated *in vacuo* to a small volume and the precipitated crude ester (14.2 g., 80%) was filtered. On crystallization from a mixture of ether and petroleum ether, colorless needles were obtained melting at 111–112°.

Anal. Calcd. for $C_{16}H_{17}ClN_2O_2$: C, 63.05; H, 5.62. Found: C, 62.68; H, 5.36.

7-Chloro-1-methyl-5-phenyl-3H-1,4-benzodiazepin-2(1H)-one 4-oxide (XIIIa). To a stirred warm solution of 15 g. (52.5 moles) of 7-chloro-5-phenyl-3H-1,4-benzodiazepin-2(1H)-one 4-oxide (III) in 700 cc. of methanol were added 2.78 g. (52.5 moles) of sodium methoxide, and, after 5 min., 5 cc. (52.5 moles) of dimethyl sulfate. The reaction mixture was refluxed for 1 hr., concentrated *in vacuo* to a small volume and diluted with ether and petroleum ether. The formed crystals (11 g., 70%) were filtered and washed with water. After recrystallization from acetone, colorless prisms melting at 188–189° were obtained.

Anal. Calcd. for $C_{16}H_{13}N_2O_2Cl$: C, 63.90; N, 4.36; Found: C, 64.07 N, 4.30.

7-Chloro-1-ethyl-5-phenyl-3H-1,4-benzodiazepin-2(1H)-one (XIIIb). To a suspension of 5.75 g. of 7-chloro-5-phenyl-3H-1,4-benzodiazepin-2(1H)-one 4-oxide (III) in 150 cc. dry benzene was added 1.08 g. of sodium methoxide. About 10 cc. of the solvent containing some methanol was distilled. Ethyl bromide (2.34 cc.) was then added and the mixture was refluxed for 20 hr. The reaction mixture was then diluted with ice water, the organic layer was separated, dried, and concentrated *in vacuo*. The oily residue was crystallized from a mixture of methylene chloride and petroleum ether and yielded 3.7 g. of crude reaction product melting at 203–204.° Upon recrystallization from a mixture of acetone and petroleum ether the pure ethyl derivative formed colorless plates melting at 207–208°.

Anal. Calcd. for $C_{17}H_{15}N_2O_2Cl$: C, 64.86; H, 4.80. Found: C, 64.95; H, 4.64.

1-Allyl-7-chloro-5-phenyl-3H-1,4-benzodiazepin-2(1H)-one 4-oxide (XIIIc). To a solution of 5.4 g. (0.02 mole) of 7-chloro-5-phenyl-3H-1,4-benzodiazepin-2(1H)-one 4-oxide in 300 cc. of benzene was added 1.08 g. (0.02 mole) of sodium methoxide. Benzene (100 cc.) was distilled in order to remove the liberated methanol; then 1.73 cc. (0.02 moles) of allyl bromide was added. The solution was refluxed for 2.5 hr., then washed with water, dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residue crystallized from a mixture of acetone and petroleum ether in colorless plates melting at 150–151°. The yield was 1.8 g.

Anal. Calcd. for $C_{18}H_{15}N_2O_2Cl$: C, 66.16; H, 4.63. Found: C, 66.08; H, 4.87.

1-Benzyl-7-chloro-5-phenyl-3H-1,4-benzodiazepin-2(1H)-one 4-oxide (XIIId). To a warm, stirred suspension of 28.6 g. (0.1 mole) of 7-chloro-5-phenyl-3H-1,4-benzodiazepin-2(1H)-one 4-oxide (III) in 450 cc. of dry benzene was added 5.4 g. of sodium methoxide. The mixture was refluxed and part of the solvent was distilled to remove the liberated methanol. To this clear solution were added 11.5 cc. of benzyl chloride, 1 g. of sodium iodide, and 200 cc. of acetonitrile. The mixture was refluxed for 15 hr., then concentrated *in vacuo* to a smaller volume and diluted with water. The benzene layer was separated, dried over sodium sulfate, and filtered. The filtrate was concentrated *in vacuo* and the oily residue dissolved in a small amount of a mixture of equal parts (by volume) of methylene chloride and petroleum ether. This was adsorbed on a column (3.5 cm. diameter) prepared with 450 g. of activated aluminum oxide and the above mixture of solvents. The elution with 2 l. of the same solvent mixture removed impurities.

The reaction product was eluted first with 2 l. of methylene chloride and then with 500 ml. of methylene chloride containing 10% methanol. These two eluates were combined and concentrated *in vacuo* to dryness. The residue was crystallized from a mixture of methylene chloride, ether and petroleum ether, yielding 15 g. (40%) of the crude reaction product. The pure product formed, after crystallization from methylene chloride, colorless prisms melting at 151–152°.

Anal. Calcd. for $C_{22}H_{17}N_2O_2Cl$: C, 70.12; H, 4.55. Found: C, 70.31; H, 4.39.

7-Chloro-1-methyl-5-phenyl-3H-1,4-benzodiazepin-2-(1H)- (Xa). A. A mixture of 3 g. (0.01 mole) of 7-chloro-1-methyl-5-phenyl-3H-1,4-benzodiazepin-2-(1H)-one 4-oxide (XIII a), 30 cc. of chloroform and 1 cc. of phosphorus trichloride was refluxed for 4 hr. The reaction mixture was then poured on ice and stirred with an excess of 40% sodium hydroxide solution. The chloroform solution was separated, dried with sodium sulfate, filtered and concentrated *in vacuo*. The residue was dissolved in methylene chloride and crystallized by the addition of petroleum ether yielding 1.8 g. (63%) of the crystalline reaction product melting at 120–122°. After recrystallization from a mixture of acetone and petroleum ether, the product formed colorless plates melting at 125–126°.

The same compound was also formed in almost quantitative yield by catalytic hydrogenation of XIII a in methanol at atmospheric pressure (30–50°) using Raney nickel as catalyst.

Anal. Calcd. for $C_{16}H_{13}N_2OCl$: C, 67.49; H, 4.60. Found: C, 67.25; H, 4.33.

B. To a solution of 5.4 g. (0.02 mole) of 7-chloro-5-phenyl-3H-1,4-benzodiazepin-2(1H)-one (IV) in 300 cc. of benzene was added 1.08 g. (0.02 moles) of sodium methoxide. Benzene (100 cc.) was distilled in order to remove the liberated methanol; then 1.9 cc. (0.02 mole) of dimethyl sulfate was added. The solution was refluxed for 1 hr., then washed with water, dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residue crystallized from a mixture of ether and petroleum ether. The yield was 50%.

7-Chloro-1-ethyl-5-phenyl-3H-1,4-benzodiazepin-2(1H)-one (Xb). A solution of 4 g. of 7-chloro-1-ethyl-5-phenyl-3H-1,4-benzodiazepin-2(1H)-one 4-oxide (XIIIb) in 180 cc. of methanol was hydrogenated in the presence of 5 g. of wet Raney nickel at room temperature and atmospheric pressure. The uptake stopped after the absorption of 1 mole of hydrogen. The mixture was then filtered and the solution concentrated *in vacuo* to dryness. The oily residue was crystallized from acetone and yielded 2.8 g. of crude reaction product. An additional crystallization from acetone gave the pure product forming colorless prisms melting at 127–128°.

Anal. Calcd. for $C_{17}H_{15}N_2OCl$: C, 68.34; H, 5.06. Found: C, 68.55; H, 4.76.

1-Benzyl-7-chloro-5-phenyl-3H-1,4-benzodiazepin-2(1H)-one (Xd). A solution of 7.5 g. of 1-benzyl-7-chloro-5-phenyl-3H-1,4-benzodiazepin-2(1H)-one 4-oxide (XIII d) in 110 cc. of methanol was hydrogenated in the presence of 5 g. of wet Raney nickel at room temperature and atmospheric pressure. The uptake stopped after the absorption of 1 mole of hydrogen. The mixture was filtered, the solution concentrated *in vacuo* to small volume, and 4.5 g. of crude crystalline reaction product was filtered. Upon recrystallization from a mixture of methylene chloride, ether, and petroleum ether, the pure product formed colorless prisms melting at 174–175°.

Anal. Calcd. for $C_{22}H_{17}N_2OCl$: C, 73.23; H, 4.75. Found: C, 72.92; H, 4.68.

1-Chloro-1-hydroxymethyl-5-phenyl-3H-1,4-benzodiazepin-2(1H)-one (Xe). A solution of 16.2 g. of 7-chloro-5-phenyl-3H-1,4-benzodiazepin-2(1H)-one (IV), 2.7 g. of paraformaldehyde, and 0.1 g. of sodium hydroxide in 265 cc. of 95% alcohol was refluxed for 8 hr. and then concentrated *in vacuo* to a small volume. Water (100 cc.) was added and 7.2 g. of crystalline starting material was filtered. The filtrate was concentrated *in vacuo* to smaller volume and extracted with methylene chloride. The methylene chloride extract was dried over sodium sulfate and concentrated *in vacuo*. To the oily residue ether was added and the reaction product which crystallized out was filtered. The yield of the crude reaction product was 4.7 g. Upon recrystallization from a mixture of methanol, ether, and petroleum ether, the pure product formed colorless prisms melting at 201–202°.

Anal. Calcd. for $C_{16}H_{13}N_2O_2Cl$: C, 63.90; H, 4.32. Found: C, 63.80; H, 4.40.

Acknowledgment. We are indebted to Dr. L. O. Randall and his co-workers for the pharmacological data, to Dr. A. Motchane, Mr. S. Traiman, and Dr. V. Toome for the infrared and ultraviolet spectra, and to Dr. Al Steyermark and his staff for the microanalysis. Mr. L. A. Dolan was helpful in the preparation of larger amounts of starting materials and intermediates.

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Synthesis of Heterocyclic-Substituted Chromones and Chalcones

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Received June 22, 1961

The preparation of eleven new 2-heterocyclic-substituted chromones and of five new related chalcones is reported. Condensation of 2′-hydroxyacetophenones with heterocyclic acid chlorides, Baker-Venkataraman rearrangement of the products, followed by dehydration gave the chromones III. Base-catalyzed condensation of 2′-hydroxyacetophenones with heterocyclic aldehydes yielded the chalcones IV.

In recent years increasing attention has been directed to the biological activity of chromones and chalcones. Broncho-dilatory[1] and coronary spasmolytic[2] properties have been reported for various chromones, especially those having heterocyclic substituents in the 2-position, while related chalcones have exhibited bacteriostatic,[3] tuberculostatic,[4] and insecticidal[5] activity.

This paper describes the preparation of a number of new heterocyclic-substituted chromones and some of the corresponding chalcones, together with some previously reported in the literature but now synthesized by a different method. All the compounds reported have been tested for antitumor activity by the National Institutes of Health, Bethesda, Md., and some for cardiovascular activity by the Lilly Research Laboratories, Indianapolis, and the Smith Kline & French Laboratories of Philadelphia.

Synthesis of chromones of this type has most frequently been accomplished by a Claisen condensation of 2′-hydroxyacetophenones with the ethyl esters of heterocyclic acids, followed by dehydration.[2] Oxidative ring-closure of 2′-hydroxychalcones with selenium dioxide has also been employed.[6] A further method[7] adopted in the present work has

TABLE I

2′-ACYLOXYACETOPHENONES

Compound	M.P.	Yield, %	Calcd., %	Found, %
2′-Nicotinyloxyacetophenone	88–89	90	C, 69.7; H, 4.6; N, 5.8	C, 69.4; H, 4.6; N, 5.2
2′-Isonicotinyloxyacetophenone	80–81	30	C, 69.7; H, 4.6; N, 5.8	C, 69.5; H, 4.8; N, 5.8
4′-Methoxy-2′-nicotinyloxyacetophenone	89–90	20	C, 66.4; H, 4.8; N, 5.2	C, 66.6; H, 4.8; N, 5.4
2′-Isonicotinyloxy-4′-methoxyacetophenone	75–76	15	C, 66.4; H, 4.8; N, 5.2	C, 66.5; H, 5.0; N, 4.9
5′-Methoxy-2′-nicotinyloxyacetophenone	78–80	91	C, 66.4; H, 4.8; N, 5.2	C, 66.8; H, 4.9; N, 5.1
2′-Isonicotinyloxy-5′-methoxyacetophenone	84–85	81	C, 66.4; H, 4.8; N, 5.2	C, 66.4; H, 4.8; N, 5.1
4′,6′-Dimethoxy-2′-nicotinyloxyacetophenone	123–124	83	C, 63.8; H, 5.0; N, 4.6	C, 63.5; H, 5.3; N, 4.4
2′-Isonicotinyloxy-4′,6′-dimethoxyacetophenone	121–122	79	C, 63.8; H, 5.0; N, 4.6	C, 63.5; H, 5.2; N, 4.9
3′,4′-Dimethoxy-2′-nicotinyloxyacetophenone	118–119	71	C, 63.8; H, 5.0; N, 4.6	C, 63.9; H, 5.0; N, 4.7
2′-Isonicotinyloxy-3′,4′-dimethoxyacetophenone	120–121	52	C, 63.8; H, 5.0; N, 4.6	C, 63.8; H, 4.9; N, 4.8
2′-Quinaldyloxyacetophenone	140–141	47	C, 74.2; H, 4.5; N, 4.8	C, 74.2; H, 4.7; N, 4.6
2′-(2-Furoyloxy)-4′-methoxyacetophenone	113–114	95	C, 64.6; H, 4.7	C, 64.3; H, 4.6
2′-(2-Furoyloxy)-5′-methoxyacetophenone	70–71	77	C, 64.6; H, 4.7	C, 64.4; H, 4.5
2′-(2-Furoyloxy)-6′-methoxyacetophenone	87–89	84	C, 64.6; H, 4.7	C, 64.6; H, 4.7
2′-(2-Thenoyloxy)acetophenone	112–114	83	C, 63.4; H, 4.1; S, 13.0	C, 63.1; H, 4.2; S, 12.6
4′-Methoxy-2′-(2-thenoyloxy)acetophenone	88–89	94	C, 60.9; H, 4.4; S, 11.6	C, 60.4; H, 4.2; S, 12.0
5′-Methoxy-2′-(2-thenoyloxy)acetophenone	75–77	95	C, 60.9; H, 4.4; S, 11.6	C, 60.9; H, 4.6; S, 11.3
6′-Methoxy-2′-(2-thenoyloxy)acetophenone	90–91	96	C, 60.9; H, 4.4; S, 11.6	C, 61.0; H, 4.4; S, 11.0

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