styrene (uninhibited) were obtained from Eastman Kodak Co. and *cis*-stilbene from the Aldrich Chemical Co. Toluene was Baker Analyzed Reagent grade. In all cases, purity was confirmed by glpc analysis.

Pyrolysis Procedure.—Solid samples (1-g quantities) were pyrolyzed in ceramic boats; liquid samples were injected directly onto the hot surface of the pyrolysis tube which was packed with quartz chips for each pyrolysis. Volatile products were collected in three traps cooled in Dry Ice–acetone and one gas scrubber filled with ether. Alkali (0.5% aqueous NaOH) was used as an additional scrubber when acidic products were expected (*e.g.*, pyrolysis of cinnamic acid, sodium cinnamate).

Maximum contact time varied from 1 to 2 sec generally and was taken to be the interval between sample introduction into the preheated pyrolysis tube and completion of the pyrolysis as indicated by cessation of gas evolution.

Traps were washed with ether, and when necessary with 0.5% aqueous NaOH. Successive adjustments of the aqueous alkaline extract first to pH 6.5 and then to pH 1.5 with 25% sulfuric acid liberated possible phenolic and acidic products, respectively, which were in turn removed with ether. The three ether solutions, neutrals, phenols and acids, were each concentrated by rotary evaporation and examined by glpc.

No phenols were found in any of the products. Acids were gas chromatographed as their trimethylsilyl esters.[36] All identifications were made by comparing the ultraviolet and infrared absorption spectra of collected peak effluents with those of known compounds, and confirmed by co-injection studies. Phenylnaphthalene identification was further confirmed by mass spectral analysis. Relative concentrations were determined by internal normalization.[37] Individual peak areas were measured by triangulation.[37]

(36) T. C. Jones and I. Schmeltz, *Tobacco Sci.*, **12**, 10 (1968).

(37) H. Purnell, "Gas Chromatography," John Wiley & Sons, Inc., New York, N. Y., 1962, p 398.

Registry No.—*trans*-Cinnamic acid, 140-10-3; sodium *trans*-cinnamate, 18509-03-0; styrene, 100-42-5; distyryl, 886-65-7; *cis*-stilbene, 645-49-8; *trans*-stilbene, 103-30-0.

Acknowledgment.—We thanks Messrs. C. J. Dooley and J. W. Hampson for assistance with the mass spectral and differential scanning calorimetry measurements, respectively. We also wish to thank Drs. A. R. Day and L. J. Steffa for their comments and advice in preliminary reviews.

Quinazolines and 1,4-Benzodiazepines. XLIV.[1a] The Formation of Isoindoles by the Ring Contraction of 1-Alkyl-1,4-benzodiazepines[1b]

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1-Alkyl-substituted 2,3-dihydro-5-phenyl-(2H)-1,4-benzodiazepin-2-ones of type **1** have been shown to undergo almost quantitative rearrangement to give N-alkyl-3-phenyl-1-isoindolecarboxamides of type **2** on treatment with base in nonaqueous media. A number of transformation products are described and possible mechanisms for the rearrangement are discussed.

Our interest in the chemistry of 1,4-benzodiazepine derivatives[2] prompted us to investigate the reactivity of the sodium salt of the anion of 7-chloro-2,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (**1**) and some of its analogs.

It was found that, by treating a solution of **1** in dimethylformamide with sodium hydride, hydrogen was evolved and a blood red solution of the 3-sodio derivative was formed. At temperatures approximating 0° and in a dry, inert atmosphere, this solution could be kept for many hours. As the solution was allowed to warm, an exothermic reaction took place and the mixture yielded the isoindole **2**.

The structure of the isoindole was corroborated both by its chemical reactions and by a comparison of some of its derivatives with authentic specimens. Basic peroxide oxidation of **2** gave an excellent yield of a mixture of the known 4-chloro-2-benzoylbenzoic acid **3**[3] and its cyclic amide, the phthalimidine **4**. Acetylation with acetic anhydride in the presence of boron trifluoride gave a mixture of the monoacetyl derivative **5** and its dehydration product, compound **6**. Mild acid hydrolysis of **6** regenerated the isoindole **2** in almost quantitative yield. Alkylation of **2** with base and methyl iodide gave a mixture of C- and N-alkylated isomers **7** and **8**. Catalytic hydrogenation of **8** gave the dehalogenated isoindoline **9**. Compound **9** was also prepared from **10** by catalytic hydrogenation and **10** in turn was obtained by the rearrangement of the 4-alkyl quaternary salt of **14**, compound **11**. An authentic sample of **10** was synthesized by treatment of the known isoindole **12**[4] with methyl isocyanate. Compound **14** was rearranged with sodium hydride in the same manner as **1** and yielded the isoindole **13** which in turn was shown to be identical with the product derived by the dehalogenation of compound **2** (Scheme I).

The isoindoles of types **2** and **13** were found to be extremely stable compounds, owing, probably, to the resonance stabilization imparted by the carboxamido function. These N-unsubstituted isoindoles could be oxidized but only with some difficulty. Thus, heating a solution of **2** in hydriodic acid under reflux for con-

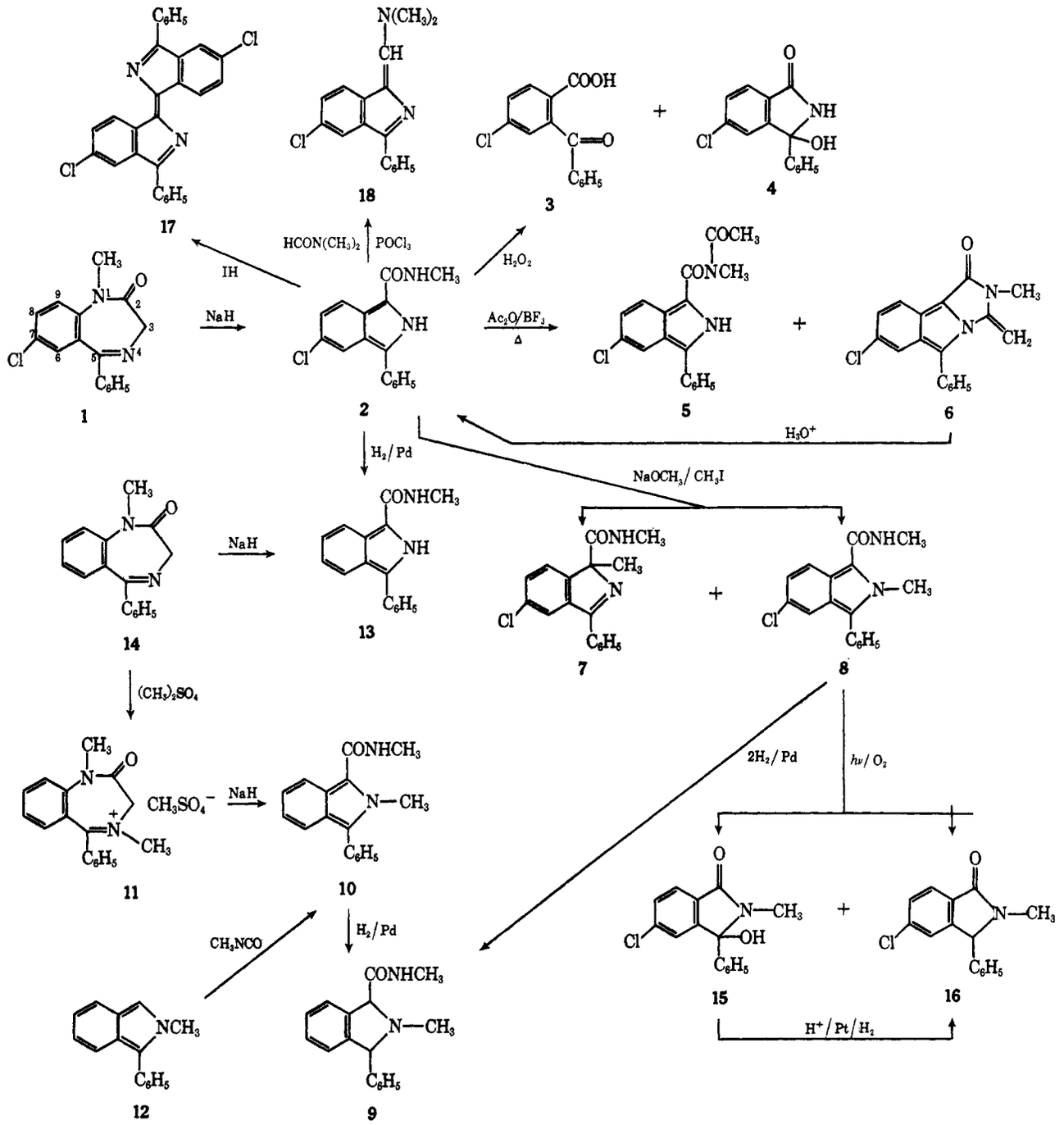
(1) (a) Paper XLIII: A. M. Felix, J. V. Earley, R. I. Fryer, and L. H. Sternbach, *J. Heterocycl. Chem.*, **5**, 731 (1968). (b) A part of this work has been reported in preliminary form: R. I. Fryer, J. V. Earley, and L. H. Sternbach, *J. Amer. Chem. Soc.*, **88**, 3173 (1966).

(2) R. I. Fryer, J. V. Earley, and L. H. Sternbach, *J. Org. Chem.*, **32**, 3798 (1967), and earlier papers.

(3) A. Ree, *Ann.*, **233**, 239 (1886).

(4) W. Theilacker and H. Kalenda, *ibid.*, **584**, 87 (1953).

SCHEME I



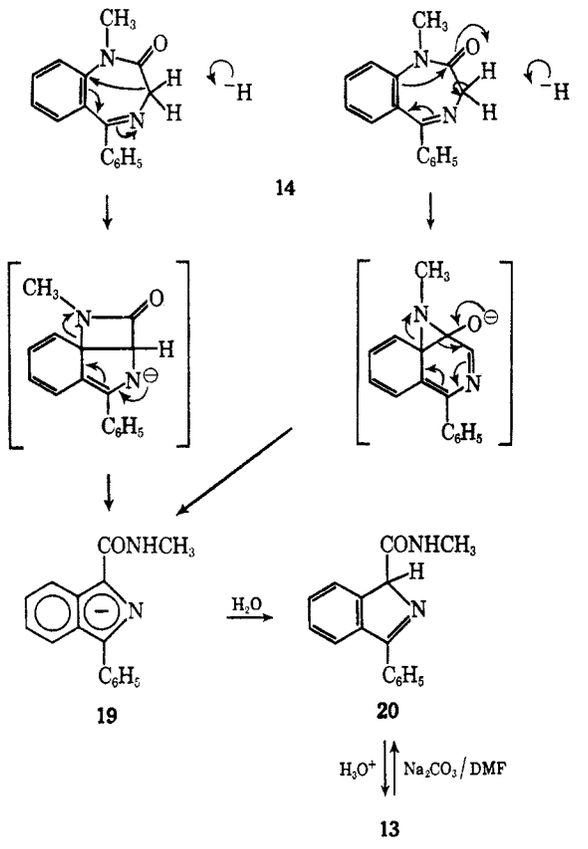
siderable periods of time afforded the bisisoindolenine **17** while similar treatment of **13** afforded the corresponding deschloro compound as previously described[5] (the configuration at the double bonds has not been established). The N-alkylation products, however, were very susceptible to air oxidation. Thus, a solution of compound **8** in the presence of light and air was rapidly converted into a mixture of the phthalimidines **15** and **16**. An authentic sample of **15** was readily prepared from the known acid **3** and was then hydrogenated to give the other oxidation product, compound **16**.

The ring contraction of 1-substituted 1,4-benzodiazepin-2-ones described in this paper can be accommodated within a mechanistic scheme which involves attack of hydride ion at the 3 position of the benzodiazepine nucleus (removal of one of the acidic protons) followed by a ring contraction to give either of the tricyclic intermediates as shown. Either intermediate could then undergo further ring contraction to give the salt of the isoindole carbanion **19** (Scheme II). The initial formation of the 3-sodio salt of the benzodiazepinone could be demonstrated by adding methyl iodide to the dimethylformamide solution and isolating, on work-up, an excellent yield of the known 3-methyl-substituted derivative.[6] When 1,4-benzodiazepin-2-ones unsubstituted in the 1 position are treated with 1 equiv of sodium hydride under the same conditions, the 1-sodio derivative is obtained. On treatment with a 2nd equiv of sodium hydride a red solution is obtained

(5) R. I. Fryer, B. Brust, J. V. Earley, and L. H. Sternbach, *J. Chem. Soc., C*, 366 (1967).

(6) L. H. Sternbach, unpublished results.

SCHEME II



which is stable even at reflux and after decomposition gives a quantitative recovery of starting material. This is also in agreement with the above mechanisms since a rearrangement of this species would require a very unlikely double negative charge on the lactam nitrogen. The previously described rearrangement of a 1-unsubstituted benzodiazepinone to an isoindole in pyridine/acetic anhydride[5] has therefore been explained by the initial formation of a 1-acetyl benzodiazepinone as the primary intermediate.

There has been much discussion as to whether isoindoles exist in the 1H or the tautomeric 2H form. Lwowski showed by nmr studies that, in solution, 1-penylisoindoles are in equilibrium with the tautomeric isoindolenine,[7] while Bender and Bonnett have reported that 1,3,4,7-tetramethylisoindole exists mainly as the isoindolenine tautomer.[8] For the first time we have been able to isolate both possible tautomers of an isoindole. By treating a solution of **13** in dimethylformamide with sodium carbonate we obtained the isoindolenine **20.** Structure **20** is preferred to the other possible insoindolenine structure on the basis of the shift in frequency of the carbonyl absorbtion in the ir spectrum and the chemical shift of the methyl group protons in the nmr spectrum when compared with the corresponding spectrum of compound **13.** Thus, for compound **20** and for compound **13,** respectively, the ir spectra show $\nu_{C=O}^{CHCl_3}$ 1680 and 1530 cm^{-1} and $\nu_{C=O}^{CHCl_3}$ 1630 and 1540 cm^{-1}, and the nmr spectral show δ_{CDCl_3} 2.65 (3 H doublet, J = 5 cps, $NHCH_3$) and $\delta_{DMF\text{-}d_7}$ 3.01 (3 H doublet, J = 5 cps, $NHCH_3$).

These shifts indicate that, in **20,** the $CONHCH_3$ group is attached to a saturated center of the isoindolenine nucleus.

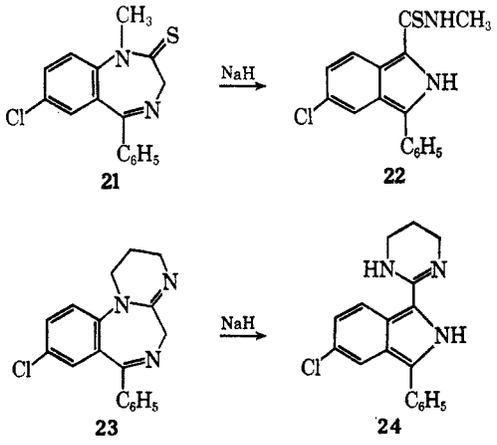
The same type of shifts were observed in the C-alkylation products and thus compound **7** was assigned the structure shown. Further evidence for this assignment is given by the rather unusual type of Vilsmeier reaction product **18** obtained by treatment of **2** with phosphorus oxychloride and dimethylformamide. Here again, C alkylation takes place at the 1 position followed, presumably, by the elimination of a carboxamido group rather than the usual proton.

The substituent in the 5 position of the isoindole greatly affected the ratio of C- to N-alkylation products and, while the ratio was approximately 2:1 when the substituent was chlorine (compounds **7** and **8**), for the 5-nitro compound[9] the ratio was 1:12 and for hydrogen 1:0. Therefore, as the substituent becomes more electron withdrawing, we obtained more of the N-alkylated material probably owing to a change in the charge distribution of the anion. For the same reason we were unable to convert the 5-substituted isoindoles into the corresponding isoindolenines under the conditions used for the preparation of **20.**

This isoindolenine **20** could be quantitatively reconverted into the thermodynamically more stable isoindole **13,** simply by treatment with acid or with strong aqueous base.

The rearrangement of 1-substituted benzodiazepines was found to be quite general and, besides a number of analogs, the thione **21** and the tetrahydropyrimido-[1,2-*a*]1,4-benzodiazepine **23**[10] were both converted in excellent yield into the corresponding isoindoles **22** and **24,** respectively (Scheme III).

SCHEME III



Experimental Section[11]

5-Chloro-N-methyl-3-phenyl-1-isoindolecarboxamide (2).—A solution of 171 g (0.6 mol) of 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (**1**)[12] in 500 ml of dry N,N-

(7) D. F. Veber and W. Lwowski, *J. Amer. Chem. Soc.*, **86**, 4152 (1964).
(8) C. O. Bender and R. Bonnett, *Chem. Comm*, **198**, (1966).

(9) Prepared from 1,3-dihydro-7-nitro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one [L. H. Sternbach, R. I. Fryer, O. Keller, W. Metlesics, G. Sach, and N. Steiger, *J. Med. Chem.*, **6**, 261 (1963)] by treatment with sodium hydride in dimethylformamide as described for the preparation of compound **2.**
(10) M. E. Derieg, R. Schweininger and R. I. Fryer, *ibid.*, **11**, 912 (1968).
(11) All melting points were determined microscopically on a hot stage and are corrected. The uv spectra were determined in 2-propanol on a Cary Model 14 spectrophotometer, nmr spectra with a Varian A-60 instrument, ir spectra on a Beckman IR-9 spectrophotometer, and mass spectra with a CEC 21-110 spectrometer. Petroleum ether refers to a fraction of bp 30–60°.
(12) L. H. Sternbach and E. Reeder, *J. Org. Chem.*, **26**, 4936 (1961).

dimethylformamide was treated with 27.6 g (0.69 mol) of a 60% dispersion of sodium hydride in mineral oil. The blood red solution was warmed to 75° when the mixture turned brown. The solution was cooled to room temperature when 50 ml of water was carefully added. The reaction mixture was next treated with 3 l. of water and enough 3 *N* hydrochloric acid to adjust the pH to 6. The precipitate was filtered and washed with ethanol and then ether to give 127.8 g (74.8%) of **2** as pale yellow rods, mp 204–206°. Recrystallization from chloroform afforded the analytically pure material: mp 204–206°; ir absorption ($CHCl_3$) at 3475, 3425 (NH), and 1610 and 1530 cm^{-1} (amide II C=O); uv max at 261 mμ (ε 40,500), 296 (8100), and 370 (19,450); nmr peaks (DMF-d_7) at δ 3.00 (3 H doublet, J = 5 cps, $NHCH_3$).

Anal. Calcd for $C_{16}H_{13}ClN_2O$: C, 67.49; H, 4.00; Cl, 12.50. Found: C, 67.39; H, 4.69; Cl, 12.55.

4-Chloro-2-benzoylbenzoic Acid (3) and 5-Chloro-3-hydroxy-3-phenylphthalimidine (4).—A solution of 3.0 g (10.5 mmol) of **2** in 150 ml of ethanol was cooled to 0° and treated with 18 ml of 30% hydrogen peroxide followed by the dropwise addition of 45 ml of a 10 *N* solution of sodium hydroxide. The mixture was allowed to stand at room temperature for 1 hr and was then heated under reflux for 15 min. Ethanol was removed under reduced pressure, and the solution was first acidified with concentrated hydrochloric acid and then made basic with ammonium hydroxide. The solution was extracted with 100 ml of ether, which was reserved, acidified to pH 4–5, and extracted again with 100 ml of ether. The second ether fraction was washed with 75 ml of saturated brine, dried over anhydrous sodium sulfate, and evaporated to give 0.4 g of **3** as white prisms, mp and mmp[3] 170–181°.

The first ether extract was evaporated to dryness, 15 ml of concentrated hydrochloric acid was added, and the white precipitate, obtained by filtration, was recrystallized from a mixture of dichloromethane and hexane to give an additional 0.5 g of **3** as white prisms, mp and mmp 170–183°.

The filtrates were evaporated to dryness and dissolved in 100 ml of ether. The solution was washed with 100 ml of dilute ammonium hydroxide and 75 ml of saturated brine, dried over anhydrous sodium sulfate, and evaporated to dryness. The residue was crystallized from a mixture of methanol and petroleum ether to give 0.6 g (22%) of **4** as white prisms, mp 205–218°.

Anal. Calcd for $C_{14}H_{10}ClNO_2$: C, 64.75; H, 3.88; N, 5.39. Found: C, 64.47; H, 3.93; N, 5.53.

This product was shown to be identical with a sample prepared by treatment of the cyclic acid chloride of **2** with ammonia.

N-(5-Chloro-3-phenyl-2-isoindoyl)-N-methylacetamide (5) and 7-Chloro-2,3-dihydro-2-methyl-3-methylene-5-phenyl-1H-imidazo[5,1-*a*]isoindol-1-one (6).—A solution of 1.5 g (0.005 mol) of **2** in 15 ml of acetic anhydride was treated with 1 drop of boron trifluoride etherate and was warmed to 60° for 6 hr with stirring. The precipitate obtained by filtration was added to 100 ml of dilute ammonium hydroxide and extracted into two 50-ml portions of dichloromethane. The organic layers were combined, washed with saturated brine, dried over anhydrous sodium sulfate, and evaporated to dryness. The product was recrystallized from a mixture of dichloromethane and hexane to give 0.4 g (25%) of **6** as orange rods: mp 198–203°; ir absorption ($CHCl_3$) at 1710 cm^{-1} (C=O); uv max at 223 mμ (ε 23,500), 270 (22,200), 333 (6250), and 413 (6150); nmr peaks ($CDCl_3$) at δ 3.18 (3 H singlet NCH_3), 4.17 and 4.70 (2 H, AB quartet, J = 5 cps, $=CH_2$).

Anal. Calcd for $C_{18}H_{13}ClN_2O$: C, 70.02; H, 4.24; N, 9.07. Found: C, 69.97; H, 4.32; N, 9.11.

The acetic anhydride filtrates above were made basic with ammonium hydroxide and extracted with two 75-ml portions of dichloromethane. The organic layers were combined, washed with saturated brine, dried over anhydrous sodium sulfate, and evaporated to dryness. The residue was recrystallized from a mixture of dichloromethane and hexane to give 0.6 g (35%) of **5** as yellow needles: mp 170–180° dec; ir absorption ($CHCl_3$) at 3400 (NH), 1680 and 1620 cm^{-1} (C=O); mass spectrum m/e 326 and 253 [$HN(COCH_3)CH_3$]; uv max at 264 mμ (ε 23,500) and 392 (27,500); nmr peaks (DMF-d_7) at δ 2.2 (3 H singlet, $COCH_3$) and 3.33 (3 H singlet, NCH_3).

Anal. Calcd for $C_{18}H_{15}ClN_2O_2$: C, 66.16; H, 4.63; N, 8.57. Found: C, 66.20; H, 4.76; N, 8.51.

5-Chloro-N,1-dimethyl-3-phenyl-1H-isoindole-1-carboxamide (7) and 5-Chloro-N,2-dimethyl-3-phenyl-1-isoindolcarboxamide (8).—A solution of 85.5 g (0.3 mol) of **2** in 175 ml of N,N-dimethylformamide was treated with 99.2 ml of a 3.63 *M* solution of sodium methoxide in methanol. After 30 min, the solution was cooled in an ice bath and treated by the dropwise addition of 37.4 ml (0.6 mol) of methyl iodide. The mixture was kept at room temperature for 2 hr and at 50° for 0.5 hr and then poured into 1 l. of cold water. The precipitate was recovered by filtration, washed with water, and dissolved in 250 ml of dichloromethane. The organic solution was washed with 100 ml of saturated brine, dried over anhydrous sodium sulfate, and evaporated. The residue was crystallized from a mixture of dichloromethane and ether and then from dichloromethane and hexane to give 10.1 g of **8** as white needles: mp 218–219°; ir ($CHCl_3$) 3460 (NH), 1640, and 1520 cm^{-1} (amide II C=O); uv max 226 mμ (ε 24,500), 262 (32,500), 297 (7500), and 358 (16,000); nmr peaks ($CDCl_3$) at δ 4.05 (3 H singlet, NCH_3) and 3.115 (3 H doublet, J = 5 cps, $NHCH_3$).

Anal. Calcd for $C_{17}H_{15}ClN_2O$: C, 68.34; H, 5.06. Found: C, 68.13; H, 5.13.

The aqueous filtrates were extracted with three 200-ml portions of dichloromethane. The organic layers were combined, washed with water and saturated brine, dried over anhydrous sodium sulfate, and evaporated to dryness. The residual oil was fractionally crystallized from mixtures of ether and petroleum ether or from dichloromethane and ether to give an additional 5.2 g of **8** (combined yield 15.3 g, 17%) and to give 37.8 g (42%) of **7** as white plates: mp 125–128°; ir ($CHCl_3$) 3420 (NH), 1670, and 1530 cm^{-1} (amide II C=O); uv max 252 mμ (ε 13,800); nmr peaks ($CDCl_3$) at δ 2.77 (3 H doublet, J = 5 cps, $NHCH_3$) and 1.784 (3 H singlet, CCH_3).

Anal. Calcd for $C_{17}H_{15}ClN_2O$: C, 68.34; H, 5.06. Found: C, 68.45; H, 4.91.

N,2-Dimethyl-3-phenyl-1-isoindolinecarboxamide (9). A. From 8.—A solution of 2.0 g (6.7 mmol) of **8** in 80 ml of tetrahydrofuran was treated with 0.6 g of activated charcoal, 0.2 ml of 20% palladous chloride, 0.2 g of 10% palladium on charcoal, and 2.5 g of potassium acetate and was hydrogenated. After 19 hr, hydrogen uptake had ceased and the reaction mixture was filtered and evaporated to dryness. The residual oil was crystallized from ether and gave 0.15 g of starting material. Petroleum ether was added to the filtrates to give 1.0 g (55%) of **9** as white prisms: mp 124–126°; ir ($CHCl_3$) 3375 (NH), 1675, and 1540 cm^{-1} (amide II C=O); uv max 252 mμ (ε 690), 258 (800), 264 (880), and 271 (740); nmr peaks ($CDCl_3$) at δ 4.75, 4.42 (2 H, AB quartet, J_{AB} = 3.5 cps, CHC_6H_4CH), 2.84 (3 H doublet, J = 5 cps, $NHCH_3$), and 2.48 (3 H singlet, NCH_3).

Anal. Calcd for $C_{17}H_{18}N_2O$: C, 76.66; H, 6.81. Found: C, 76.59; H, 6.85.

B. From 10.—A solution of 2.0 g (7.44 mmol) of **10** in 80 ml of tetrahydrofuran was treated with 0.6 g of activated charcoal, 2.5 g of potassium acetate, 0.2 g of 10% palladium on charcoal, and 0.2 ml of a 20% solution of palladous chloride. The mixture was hydrogenated at atmospheric pressure and at room temperature until hydrogen uptake ceased (18 hr) and was then filtered over Celite. The Celite was washed with dichloromethane. The filtrates were combined and evaporated. The residue was dissolved in 50 ml of dichloromethane and extracted into three 40-ml portions of 6 *N* hydrochloric acid. The acid fractions were combined, washed with dichloromethane, and then made basic with ammonium hydroxide. The aqueous layer was extracted with three 50-ml portions of dichloromethane which were combined, washed with saturated brine, dried over anhydrous sodium sulfate, and evaporated to dryness. The product was recrystallized from a mixture of ether and petroleum ether to give 0.45 g (22.4%) of **9** as white prisms, mp and mmp 124–127° with a sample prepared as described in procedure A above.

2,N-Dimethyl-3-phenyl-1-isoindolecarboxamide (10). A. From 12.—A solution of 20 g (96.6 mmol) of 2-methyl-3-phenylisoindole (**12**)[4] in 50 ml of benzene was treated under nitrogen with a solution of 12 g (0.22 mol) of methyl isocyanate in 25 ml of benzene. The reaction mixture was stirred for 18 hr at room temperature when solvents were removed under reduced pressure. The residual solid was triturated with ether and filtered. The filtrates were concentrated and recrystallized from a mixture of benzene and ether to give 3.6 g (14%) of **10** as pale yellow rods: mp 185–188°; ir ($CHCl_3$) 3460 (NH), 1640, and 1530 cm^{-1} (amide II C=O); uv max 222 mμ (ε 23,200), 260 (25,750), 298 (5000), 306 (5050), and 356 (19,000); nmr peaks ($CDCl_3$) at

δ 4.08 (3 H singlet, NCH_3) and 3.05 (3 H doublet, J = 5 cps, $NHCH_3$).

Anal. Calcd for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10. Found: C, 77.59; H, 5.85.

B. From 11.—A solution of 2.0 g (5.3 mmol) of **11** in 10 ml of dry N,N-dimethylformamide under nitrogen was treated with 0.21 g (0.0053 mol) of a 60% sodium hydride dispersion in mineral oil. The solution was allowed to stir at room temperature overnight when it was poured into 150 ml of water. The precipitate was recovered by filtration and dissolved in 50 ml of dichloromethane. The dichloromethane solution was washed with 50 ml of water and 25 ml of saturated brine, dried over anhydrous sodium sulfate, and evaporated to dryness. The residue was crystallized from ether and then recrystallized from a mixture of benzene and ether to give 0.2 g (14%) of **10** as pale yellow rods, mp and mmp 185–188° with a sample prepared as described in method A.

1,3-Dihydro-1,4-dimethyl-2-oxo-5-phenyl-2H-1,4-benzodiazepin-4-ium Methyl Sulfate (11).—A solution of 6.0 g (0.024 mol) of 1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (**14**)[13] in 50 ml of benzene was treated with 6.0 g (0.048 mol) of dimethyl sulfate, and the solution was heated under reflux for 2 hr, cooled, and filtered. The precipitate was recrystallized from a mixture of methanol and ether to give 8.2 g (91%) of **11** as white rods, mp 176–180°.

Anal. Calcd for $C_{18}H_{20}N_2O_5S$: C, 57.43; H, 5.35. Found: C, 57.41; H, 5.45.

N-Methyl-3-phenyl-1-isoindolecarboxamide (13). A. From 2.—A solution of 5 g (17.5 mmol) of **2** in 200 ml of tetrahydrofuran was mixed with 1.2 g of activated charcoal, 3.6 g of potassium acetate, 0.3 ml of a 20% solution of palladous chloride, and 0.6 g of a 10% palladium-on-carbon catalyst. Hydrogenation at atmospheric pressure and room temperature was allowed to proceed until approximately 1.3 molar equiv of hydrogen had been adsorbed. Hydrogenation was stopped, the solution was filtered, and the solvents were removed under reduced pressure. The residue was dissolved in 300 ml of dichloromethane, which was washed with 100 ml of 0.5 *N* hydrochloric acid and 100 ml of saturated brine, dried over anhydrous sodium sulfate, and evaporated to dryness. The product was recrystallized from chloroform to give 2 g (45%) of **13** as white rods: mp 218–220°; ir ($CHCl_3$) 3480, 3420 (NH), 1630, and 1540 cm^{-1} (amide II C=O); uv max 221 mμ (ϵ 14,600), 230 (15,200), 258 (33,000), 295 (5900), and 369 (22,500); nmr peaks (DMF-d_7) at δ 3.01 (3 H doublet, J = 5 cps, $NHCH_3$).

Anal. Calcd for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64. Found: C, 76.88; H, 5.99.

B. From 14.—To 60 g (0.24 mol) of **14**[13] in 200 ml of dry N,N-dimethylformamide under nitrogen was added 10.6 g (0.264 mol) of a 60% sodium hydride dispersion in mineral oil. The red solution was stirred for 2 hr at 40° and for 1.5 hr at 90° and then cooled in an ice bath, poured onto ice, and diluted to 3 l. with water. The precipitate was recovered by filtration and washed first with ethanol and then with ether. Recrystallization of the product from a mixture of tetrahydrofuran and ethanol gave 41 g (68%) of **14** as white rods, mp and mmp 216–220° with a sample prepared as described in A above.

5-Chloro-3-hydroxy-2-methyl-3-phenylphthalimidine (15) and 5-Chloro-2-methyl-3-phenylphthalimidine (16).—A solution of 1.0 g (3.3 mmol) of **8** in 100 ml of dichloromethane contained in a large crystallizing dish was irradiated with a short-wave uv light for 4 hr. The mixture was washed with 40 ml of saturated brine, dried over anhydrous sodium sulfate, and evaporated to dryness. The residue was dissolved in 15 ml of benzene and filtered through a sintered-glass funnel containing 75 g of silica gel. Benzene was removed to afford starting material (5%) and an unknown product (5% by tlc). The silica gel was washed with 400 ml of ether which was then concentrated to a small volume. The precipitate was recovered by filtration and recrystallized from a mixture of dichloromethane and hexane to give 0.3 g of **15** as white prisms, mp 187–189°. A second crop (0.2 g) was obtained from the mother liquors to give a combined yield of 0.5 g (56%).

Anal. Calcd for $C_{15}H_{12}ClNO_2$: C, 65.82; H, 4.42; N, 5.12. Found: C, 65.99; H, 4.68; N, 5.51.

This compound was shown to be identical with the product obtained by treating the cyclic acid chloride of **3** with methylamine.

The mother liquors were evaporated and the residue was dissolved in 10 ml of benzene and chromatographed over 75 g of silica gel. The column was eluted with 250 ml of benzene, which was discarded, followed by 500 ml of ether. The ether fraction was concentrated to a small volume and the product was obtained by filtration. Recrystallization of the precipitate from a mixture of dichloromethane and hexane gave 50 mg (6%) of **16** as white rods, mp 176–178°.

Anal. Calcd for $C_{15}H_{12}ClNO$: C, 69.91; H, 4.69. Found: C, 69.96; H, 4.53.

5-Chloro-2-methyl-3-phenylphthalimidine 16 by Reduction of 15.—A mixture of 8.8 g (0.032 mol) of **15**, 50 ml of glacial acetic acid, 50 ml of a 5% solution of hydrogen chloride in glacial acetic acid, and 0.5 g of platinum oxide was hydrogenated at room temperature and atmospheric pressure until hydrogen uptake had ceased. The solution was filtered over Celite which was washed with dichloromethane. The combined filtrates were poured into a large volume of ice, made basic with ammonium hydroxide, and extracted with two 200-ml portions of dichloromethane. The organic layers were combined, washed with water and then with saturated brine, dried over anhydrous sodium sulfate, and evaporated. The residue was recrystallized from a mixture of dichloromethane and hexane to give 6.2 g (76%) of **16**, mp and mmp 178–179° with a sample prepared by the irradiation of **8** as described above.

1,1'-Bis(5-chloro-3-phenyl-1H-isoindolylidene) (17).—A solution of 3.0 g of **2** in 35 ml of 57% hydriodic acid was heated under reflux for 18 hr. The solution was extracted with 150 ml of dichloromethane, which was washed with 100 ml of saturated brine, dried over anhydrous sodium sulfate, and evaporated to dryness. The red precipitate which remained with the sodium sulfate was dissolved in 200 ml of boiling chloroform. The chloroform solution was filtered and evaporated. The residue, in 100 ml of dichloromethane, was filtered through 75 g of Woelm neutral grade I alumina. The product was eluted with an additional 300 ml of dichloromethane. Solvent was evaporated and the residue was recrystallized from a mixture of dichloromethane and methanol to give 0.2 g of **17** as orange rods, mp 329–332°.

The original dichloromethane filtrates were filtered through 200 g of alumina, and the product was eluted with 800 ml of dichloromethane. Removal of solvent and recrystallization of the residue as above gave an additional 0.25 g of **17** for a combined yield of 0.45 g (19%): mp 329–332°; uv max 250 mμ (ϵ 42,000), 333 (13,900), and 455 (49,500).

Anal. Calcd for $C_{28}H_{16}Cl_2N_2$: C, 74.51; H, 3.57; N, 6.21. Found: C, 74.57; H, 3.71; N, 6.15.

5-Chloro-1-dimethylaminomethylene-3-phenyl-1H-isoindole (18).—A solution of 5 g (7.6 mmol) of **2** in 15 ml of dry N,N-dimethylformamide was treated with 0.13 ml of pyridine and 16.2 g (0.106 mol) of phosphorus oxychloride. The reaction was stirred at 110° for 1 hr, cooled, and poured into 300 ml of water. The precipitate was recovered by filtration, washed with water, and recrystallized from a mixture of methanol and ether to give 4.0 g (71%) of the hydrochloride of **18** as yellow rods, mp 205–210° dec.

Anal. Calcd for $C_{17}H_{15}ClN_2 \cdot HCl$: C, 63.96; H, 5.05; N, 8.77. Found: C, 63.73; H, 5.09; N, 8.70.

The free base was liberated with ammonium hydroxide and recrystallized from a mixture of dichloromethane and methanol to give **18** as yellow plates: mp 186–191°; uv max 253 mμ (ϵ 31,000), 400 (39,300), and infl 320 (6250); uv max (0.1 *N* HCl/20% 2-propanol) 255 mμ (ϵ 23,500), 273 (18,800), 413 (38,800), and infl 290 (16,130); nmr peaks (DMF-d_7) at δ 7.18–8.25 (9 H aromatic region), 3.90 (3 H singlet, NCH_3), and 3.47 (3 H singlet, NCH_3).

Anal. Calcd for $C_{17}H_{15}ClN_2$: C, 72.21; H, 5.35; N, 9.91; Cl, 12.54. Found: C, 72.41; H, 5.63; N, 9.99; Cl, 12.59.

N-Methyl-3-phenyl-1-isoindoleninecarboxamide (20).—A solution of 1.0 g (0.004 mol) of **13** and 0.5 g (4.8 mmol) of sodium carbonate in 20 ml of dry N,N-dimethylformamide was heated to 50° for 5 hr and at 85° for 1 hr. The reaction mixture was cooled, poured into 150 ml of water, and filtered. The precipitate was recrystallized from benzene to give 0.2 g of starting material, and the filtrates were evaporated and crystallized from ether. The product was collected by filtration and recrystallized from a mixture of benzene and hexane to give 0.1 g (10%) of **20** as white rods: mp 223–228° dec, mmp 190–202° with **13**; ir

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($CHCl_3$) 3410 (NH), 1680, and 1530 cm^{-1} (amide II C=O), uv max 253 mμ (ε 13,700); nmr peaks ($CDCl_3$) at δ 2.65 (3 H doublet, J = 5 cps, $NHCH_3$).

Anal. Calcd for $C_{10}H_{14}N_2O$: C, 76.78; H, 5.64. Found: C, 76.79; H, 5.34.

N,1-Dimethyl-3-phenyl-1H-isoindole-1-carboxamide.—A solution of 7.4 g (29.6 mmol) of **13** in 20 ml of N,N-dimethylformamide was treated with 9.8 ml (35 mmol) of a 3.63 *M* solution of sodium methoxide in methanol and, after 30 min, 8.4 g (59.2 mmol) of methyl iodide was added. The solution was stirred for 1 hr at room temperature and then at 45° for 15 min. The solution was allowed to stand at room temperature overnight and poured into 100 ml of water. The product was extracted into two 75-ml portions of dichloromethane, which were combined, washed with water and saturated brine, dried over anhydrous sodium sulfate, and evaporated to dryness. The product was recrystallized from a mixture of ether and petroleum ether to give 43.5 g (56.5%) of the C-methyl derivative as white plates, mp 130–134°.

Anal. Calcd for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10. Found: C, 77.44; H, 6.13.

An examination of the mother liquors by tlc indicated the presence of other, unindentified products from the alkylation but none of these corresponded to an authentic sample of the N,2-dimethyl derivative, compound **10**.

5-Nitro-N,2-dimethyl-3-phenyl-1-isoindolecarboxamide and N,1-Dimethyl-5-nitro-3-phenyl-1H-isoindole-1-carboxamide.—A solution of 3.3 g (1.12 mmol) of 5-nitro-N-methyl-3-phenyl-1-isoindole carboxamide (red needles, mp >350°[9]) in 20 ml of N,N-dimethylformamide was treated with 5.2 ml (0.00134 mol) of a 2.6 *M* solution of sodium methoxide in methanol. After 30-min stirring, 3.2 g (2.24 mmol) of methyl iodide was added, and the reaction was heated at 50–55° for 4 hr. The reaction mixture was cooled and poured into 200 ml of water. The precipitate was recovered by filtration and recrystallized first from acetone and then from a mixture of tetrahydrofuran, ether, and hexane to give 2.4 g (70%) of the N,2-dimethyl compound as yellow needles: mp 273–274°; nmr peaks (DMSO-d_6) at δ 4.1 (3 H singlet, NCH_3) and 2.95 (3 H doublet, J = 5 cps, $NHCH_3$).

Anal. Calcd for $C_{17}H_{15}N_3O_3$: C, 66.01; H, 4.89. Found: C, 66.03; H, 5.18.

The original filtrates were evaporated to dryness and crystallized from acetone with charcoal to remove 0.1 g of starting material. Hexane was added to the filtrates when the N,1-dimethyl derivative crystallized. Recrystallization of the product from a mixture of acetone and hexane gave 0.2 g (6%) of the analytically pure compound as white rods: mp 185–187°; nmr peaks ($CDCl_3$) at δ 2.82 (3 H doublet, J = 5 cps, $NHCH_3$) and 1.85 (3 H singlet, CCH_3).

Anal. Calcd for $C_{17}H_{15}N_3O_3$: C, 66.01; H, 4.89. Found: C, 66.04; H, 4.84.

5-Chloro-N-methyl-3-phenylthiono-1-isoindolecarboxamide (22).—A solution of 17.6 g (0.0585 mol) of 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepine-2-thione (**21**)[14] in 100 ml of dry N,N-dimethylformamide under nitrogen was treated with 2.8 g (0.07 mol) of a 60% dispersion of sodium hydride in mineral oil, and the mixture was heated with stirring to 106°. The exothermic reaction maintained itself at 110° for 10 min. Heating was continued at 125° for 0.5 hr; the reaction mixture was cooled to room temperature and poured into 1 l. of water. The solution was adjusted to pH 6 with hydrochloric acid and the crude product was recovered by filtration. This was dissolved in 250 ml of dichloromethane and the resulting solution was washed with 200 ml of water, dried over anhydrous sodium sulfate, and evaporated to dryness. Recrystallization from a mixture of benzene and hexane and then from a mixture of dichloromethane and ether gave 14.3 g (81.3%) of pure **22** as bright yellow rods: mp 197–201°; uv max 224 mμ (ε 21,700), 275 (20,800), 417 (17,000), infl 320 (9000), and infl 333 (7300); nmr peaks (DMSO-d_6) at δ 3.24 (3 H doublet, J = 5 cps, $NHCH_3$).

Anal. Calcd for $C_{16}H_{13}ClN_2S$: C, 63.88; H, 4.36. Found: C, 64.17; H, 4.31.

5-Chloro-3-phenyl-1-[2-(1,4,5,6-tetrahydropyrimido)]isoindole (24).—A solution of 1.0 g (0.0032 mol) of 9-chloro-1,2,3,5-tetrahydro-7-phenylpyrimido[1,2-*a*][1,4]benzodiazepine (**23**)[9] in 50 ml of dry N,N-dimethylformamide was treated with 0.192 g (0.004 mol) of a 50% mineral oil dispersion of sodium hydride and stirred for 15 min at room temperature with no apparent reaction. The reaction mixture, under dry nitrogen, was then heated at 100° for 1 hr. During heating, the initially pale yellow solution turned to a reddish brown and finally to a dark green. The hot solution was poured into 150 ml of ice water, forming a gelatinous yellow precipitate. The aqueous mixture was extracted with methylene chloride; the organic phase was washed with water several times and evaporated to an oil which on standing gave 0.8 g (80%) of a yellow crystalline solid, mp 115–125°, reset mp 208–210°. The analytical sample prepared by recrystallizations from a mixture of methylene chloride and cyclohexane gave **24** as pale yellow prisms: mp 208–210°; uv max 218 mμ (ε 20,300), 276 (20,500), 323 (12,400), and 401 (35,500).

Anal. Calcd for $C_{18}H_{16}ClN_3$: C, 69.78; H, 5.21; N, 13.56. Found: C, 70.10; H, 5.13; N, 13.56.

Registry No.—**2,** 18794-00-8; **4,** 18794-01-9; **5,** 18794-02-0; **6,** 18794-03-1; **7,** 18794-04-2; **8,** 18793-98-1; **9,** 18794-05-3; **10,** 7310-68-1; **11,** 18794-07-5; **13,** 7310-67-0; **15,** 18794-09-7; **16,** 15951-79-8; **17,** 18794-11-1; **18,** 18794-12-2; **18** HCl, 18794-13-3; **20,** 10470-60-7; **22,** 18794-35-5; **24,** 18794-16-6; N,1-dimethyl-3-phenyl-1H-isoindole-1-carboxamide, 18794-17-7; 5-nitro-N,2-dimethyl-3-phenyl-1-isoindolecarboxamide, 18794-18-8; N,1-dimethyl-5-nitro-3-phenyl-1H-isoindole-1-carboxamide, 18794-19-9.

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