THE JOURNAL OF Organic Chemistry®

VOLUME 37, NUMBER 24

DECEMBER 1, 1972

Novel Syntheses of 1,4-Benzodiazepines, Isoindolo[2,1-*d*][1,4]benzodiazepines, Isoindolo[1,2-*a*][2]benzazepines, and Indolo[2,3-*d*][2]benzazepines, Based on Use of the Strecker Reaction

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Received May 30, 1972

Strecker reactions of *N*-alkylanilines and *o*-aminobenzophenones **10a**, **23**, and **29** (R′ = CH_3) gave corresponding glycinonitriles, which were hydrogenated in the presence of activated nickel catalyst and NH_3 to give *N*-arylethylenediamines. Condensation products of **2** with phthalaldehydic acid undergo novel PPA cyclization to **4**, which are reducible with $LiAlH_4$ to **5**, whereas similar compounds **8** are converted with $LiAlH_4$ to fused hydroxyphthalimidines **9**. Keto nitrile **24** underwent catalytic hydrogenation (Ni) followed by cyclization to the known benzodiazepine **25**. Facile closure of **24** into cyanoindole **26a** followed by reduction gave the 2-aminomethylindole **26c**; such compounds have been transformed previously into benzodiazepin-2-ones **27** by oxidative ring opening and reclosure. Similar reduction of keto nitrile esters **33** leads to compounds **35**, whereas base-catalyzed cyclization of **33** gives cyanoindoles **36**, which are converted by reduction and cyclization into benzazepinones **39**. Various derivatives of secondary amino keto nitrile **12a** and oximino nitrile **18a** were prepared; **18b** and **18c** are relays on a new path to **15**. Reaction of α- (**10b**) and β- (**10c**) amino oximes with HCHO gave **14** and **13**, respectively. Amino keto esters **29** (R′ = CH_3) were obtained by esterifying acids resulting from ring opening of morphanthridine-6,11-diones **28**. Spiro compounds **31** and **34** were obtained by reaction of acids **29** (R′ = H) with HCHO and action of bases on bromoacetylamino acids **32**, respectively. Hydroxy dilactams **35a,b** were obtained from bromoacetylamino esters **32** (R′ = CH_3) with ammonia. Reactions leading from **35a,b** to **37** and **38** were found. Compound **35c** was hydrogenolyzed over Pd to **4a**.

1,4-Benzodiazepines have been studied intensively in the last decade.[1,2] However, little or no work has been directed toward synthesis of appropriately ortho-substituted anilinoacetonitriles and derived amines $ArN(R)(CH_2)_2NH_2$ as precursors of 1,4-benzodiazepines. The closure of an *o*-$N(R)CH_2COOR$-substituted benzhydrylamine to a 3-oxo-1,4-benzodiazepine has been reported.[3]

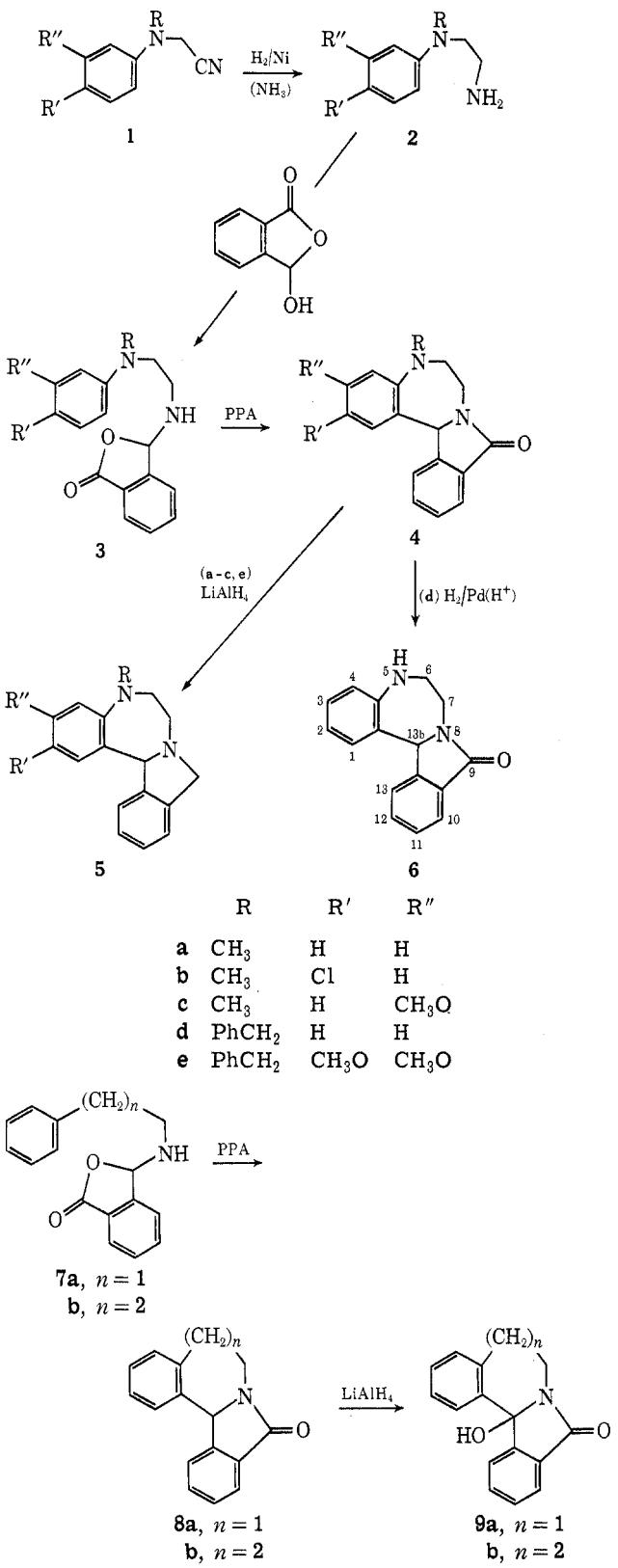
Anilines have been alkylated with α-halo esters[3] and nitriles,[4] but such reactions are difficult, particularly with weakly nucleophilic anthranilic acid and *o*-aminobenzophenone relatives. Possible approaches to introduction of an *N*-β-aminoethyl group on anilines by use of ethylene oxide, ethyleneimine, or *N*-β-bromoethylphthalimide[5] have their individual difficulties. A simple process, applicable under mild conditions and without complications to a relatively wide variety of anilines, was desired. We now report modifications of the Strecker condensation of anilines with formaldehyde and cyanide.[6-10]

In general, it was found that the so-called Knoevenagel–Bucherer method,[7] involving sequential use of formaldehyde bisulfite to prepare the water-soluble $ArN(R)CH_2SO_3^-\ Na^+$ followed by treatment with aqueous KCN to form water-insoluble anilinonitriles, is a reliable route to *N*-arylglycinonitriles from aniline, *p*-chloroaniline, aminoveratrole, and their simple *N*-alkyl derivatives. However, neither this procedure nor that used by Itoh[8] and others (starting from the aniline hydrochloride) worked as desired with less soluble *N*-benzylanilines or with weakly basic anilines ortho or para substituted by carbonyl or similar groups. For Strecker reaction in these cases, the methods devised by Marxer[9] and Dimroth,[10] using an acetic acid medium, were found to serve best.

An equally useful means for reduction of many anilinoacetonitriles to *N*-aryl ethylenediamines was found in low-pressure, nickel-catalyzed hydrogenation in ethanol in the presence of excess ammonia. Given a sufficiently active catalyst, one need not employ high pressure[8] or temperature in such reductions.

(1) G. A. Archer and L. H. Sternbach, *Chem. Rev.*, **68**, 751 (1968).
(2) L. H. Sternbach, *Angew. Chem., Int. Ed. Engl.*, **10**, 34 (1971).
(3) G. A. Archer and L. H. Sternbach, U. S. Patent 3,317,518 (1967); *Chem. Abstr.*, **65**, 16988 (1966).
(4) G. S. Sidhu, G. Thyagarajan, and M. Mazharuddin, *Indian J. Chem.*, **2**, 170 (1964).
(5) S. Gabriel, *Ber.*, **22**, 2225 (1889).
(6) D. T. Mowry, *Chem. Rev.*, **42**, 230 (1948).
(7) R. I. Buchanan and R. A. Partyka, U. S. Patent 3,517,024 (1970); *cf.* E. Knoevenagel, *Ber.*, **37**, 4059 (1904); W. M. Lauer and C. M. Langkammerer, *J. Amer. Chem. Soc.*, **57**, 2360 (1935); T. D. Stewart and C.-H. Li, *ibid.* **60**, 2782 (1938).
(8) N. Itoh, *Chem. Pharm. Bull.*, **10**, 55 (1962).
(9) A. Marxer, *Helv. Chim. Acta*, **37**, 166 (1954).
(10) K. Dimroth and H. G. Aurich, *Ber.*, **98**, 3902, 3907 (1965).

SCHEME I



Synthesis of Seven-Membered Rings by Pictet–Spengler Closure of β-Anilinoethylamine Derivatives (Scheme I).—With adequate quantities of diamines **2** on hand from reduction of Strecker nitriles **1**, we found a novel synthetic approach to dihydroisoindolo[2,1-*d*]-[1,4]benzodiazepines. Some representatives of this ring system had already been synthesized;[11] however, we had found earlier[12] that the condensation product of phthalaldehydic acid with β-phenylethylamine, **7a**, could be cyclized with PPA to fused lactam **8a**. This observation has been extended to similar synthesis of fused benzazepine and benzodiazepine rings. Condensation of diamines **2** with equivalent amounts of phthalaldehydic acid in benzene gave crude products apparently consisting (like **7a**)[12] mainly of the aminophthalides **3** (ir 5.70 μ), but probably containing also certain amounts of *N*,*N*-bis-3-phthalidyl aminoethylanilines[13] and small amounts of hydroxyphthalimidines.

Crude **3a** was cyclized with PPA at 100° to **4a** in 36% yield. Comparable yields of **4b**,**c**,**e** were obtained similarly from corresponding compounds **3**. The closure of **3d** gave a 65% yield of **4d**.

The related cyclization of **7b** to the isoindolo[1,2-*a*]-[2]benzazepine **8b** was also carried out with PPA with a longer period of heating at 100°.

These ring closures, like others of the type, presumably represent the nucleophilic attack of an aromatic ring carbon of sufficient electron density on an acyliminium moiety of sufficient reactivity. The latter originates in the very reactive phthalaldehydic acid system. During the closure of **3** to **4**, the aniline nitrogen evidently is not protonated by PPA to an extent which would suffice to obliterate the nucleophilicity of the ortho position; in the somewhat similar Meisenheimer closure of mandelylanilines to oxindoles, the fact that the nitrogen is acylated provides a similar effect. The closure to **4** fails when R = H or R = Ac in **3** because different pathways involving direct reaction of aniline N with the phthalaldiminium moiety are followed.

Ring closures of other amides, the phthalimide, homophthalimide, phenylacetamide, and α-cyanoacetamide, prepared from **2a**, with PPA or PPE at 100–200° were tried, without success.

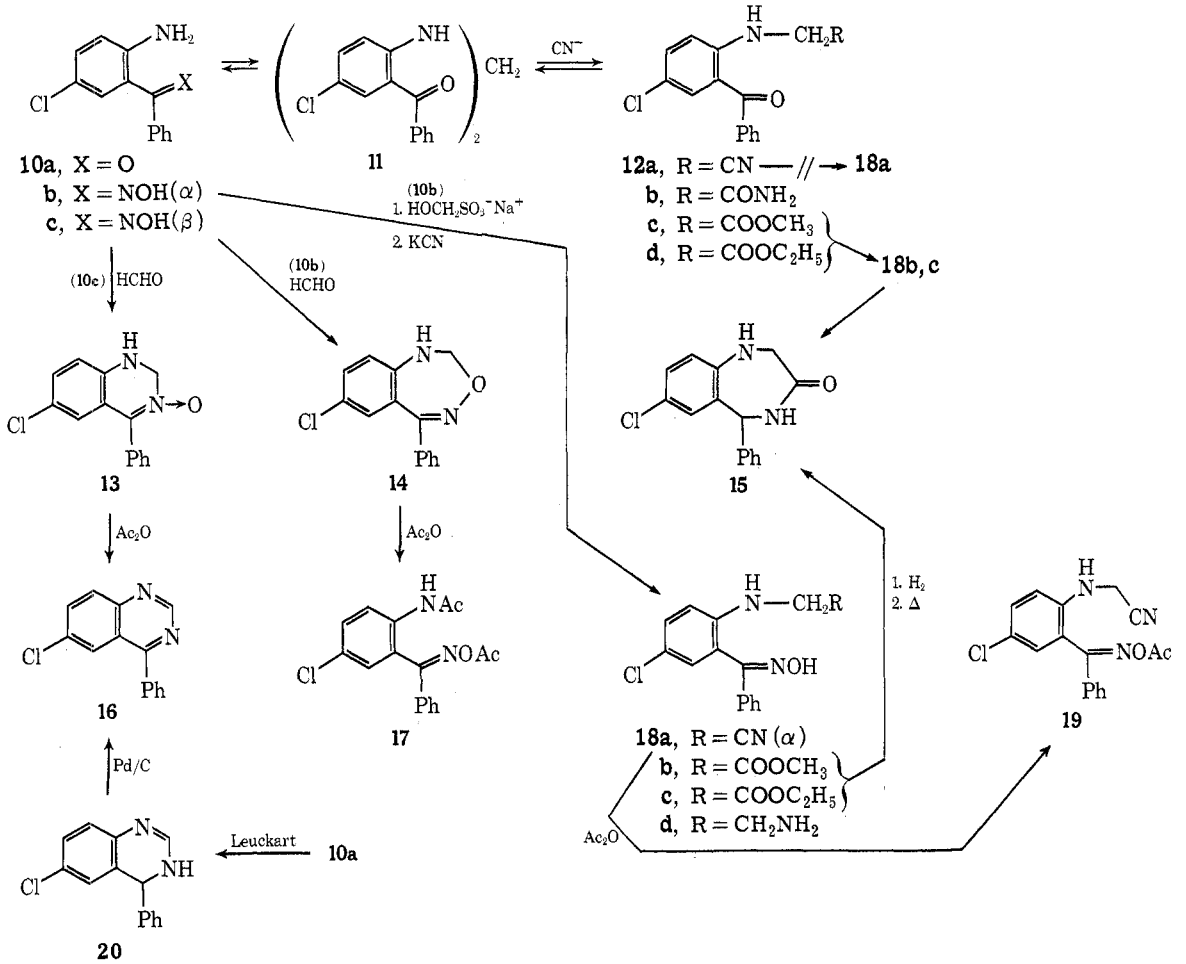
Strecker Nitriles Derived from Primary *o*-Aminobenzophenones (Scheme II).—Preliminary efforts to convert aminonitriles of this type to 2,3-dihydro-1*H*-1,4-benzodiazepines *via* reduction to diamines were not successful, but relay routes to 4,5-dihydro-1*H*-1,4-benzodiazepin-3-ones were found. The Dimroth modification of the Strecker reaction[10] was applicable to preparation of the new nitrile **12a** from the very weakly basic 2-aminobenzophenone **10a**. Slight deviations from the procedure given led to formation of the bis-aminomethylene compound **11**. Reaction of **11** with KCN in the presence of Ac_2O gave a mixture of **12a** and **21a**. The CN is a rather efficient leaving group in **12a**, since the latter reverted to **11** with ammonia and to **11** or **10b**,**c** with hydroxylamine. Amide **12b** was prepared in low yield by performing the Strecker reaction on **10a** with aqueous HCHO and KCN. Esters **12c** and **12d** could be obtained by carefully esterifying **12a**.

(11) G. E. Hardtmann and H. Ott, *J. Org. Chem.*, **34**, 2244 (1969); U. S. Patents 3,375,246 (1968); 3,465,042 (1969); 3,475,449 (1969); 3,558,648 (1971); *cf.* W. J. Houlihan, U. S. Patent 3,428, 650 (1969).

(12) G. N. Walker and R. J. Kempton, *J. Org. Chem.*, **36**, 1413 (1971). The reaction of **8a** with $LiAlH_4$ to give mainly **9a** is described in the Experimental Section of that paper.

(13) Y. Kubota and T. Tatsuno, *Chem. Pharm. Bull.*, **19**, 1226 (1971).

SCHEME II



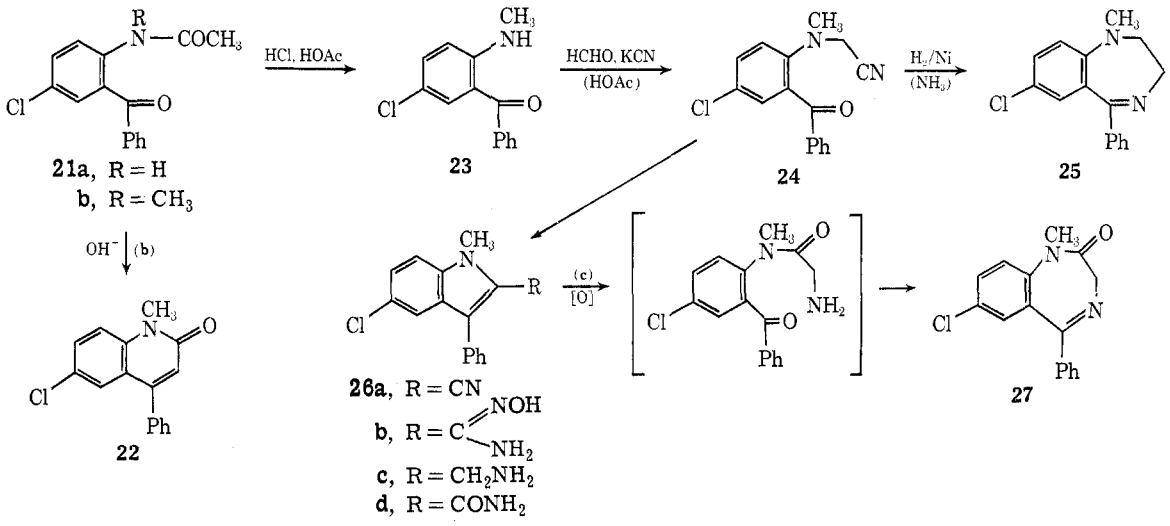
Reactions of α- and β-oximes[14,15] **10b** and **10c** with formaldehyde itself gave entirely different results. The α-oxime gave the colorless 3,1,4-benzoxadiazepine **14**, a novel compound of a class containing relatively few representatives.[14-16] The β-oxime with HCHO itself or $HOCH_2SO_3^-Na^+$ gave the yellow 1,2-dihydroquinazoline 3-oxide **13**,[17] a member of a group of compounds[18,19] which, together with 3,4-dihydro-4-arylquinazolines,[20-22] has received attention principally in connection with benzodiazepine syntheses. Interestingly, formation of **13** also was observed when **12a** and **14** were exposed to hydroxylamine and KCN, respectively. The structure of **13** was confirmed by quantitative Ac_2O-promoted Polonovski oxidation and elimination to give the quinazoline **16**, identical with a sample prepared by facile aromatization of **20**.

Strecker reaction of the β-oxime obviously was out of the question. However, using formaldehyde bisulfite on the α-oxime **10b** with DMF to dissolve the intermediate, followed by KCN treatment, we found that **18a** could be prepared. The oximino aminonitrile **18a** did not lose its CN group so readily as did **12a**. Esterification of **18a** was a more efficient route to **18b,c** than was reaction of **12c,d** with hydroxylamine. Compounds **12d** and **18c** are the same as those obtained[3] starting with the difficult $BrCH_2COOEt$ alkylation of **10a**. Compound **18c** is reported[3] to have been converted, *via* reduction to amino ester and thermal closure, to lactam **15**.

Attempts to promote intramolecular reaction under acidic conditions (HOAc, HCl, HBr) of nitrile and oximino groups in **18a** in the sense described by Taylor[23] were unrewarding, as indeed might be anticipated from the conversion of **18a** to corresponding esters **18b,c** in alcoholic HCl media. Unfortunately, the β isomer of **18a** is not available at present. However the relevant record of base-induced, retrograde reactions and ring contractions in 3-oxo-, 3-oxy-, and 3-amino-3*H*-1,4-benzodiazepines[22,24-30] may be cited in this regard.

(14) L. H. Sternbach, S. Kaiser, and E. Reeder, *J. Amer. Chem. Soc.*, **82**, 475 (1960).
(15) T. S. Sulkowski and S. J. Childress, *J. Org. Chem.*, **27**, 4424 (1962).
(16) W. Metlesics, G. Silverman, and L. H. Sternbach, *Monatsh. Chem.*, **98**, 633 (1967); *Chem. Abstr.*, **67**, 82198 (1967).
(17) G. F. Field and L. H. Sternbach, South African Patent 6,707,098 (1968); *Chem. Abstr.*, **70**, 96817 (1969).
(18) G. F. Field, W. J. Zally, and L. H. Sternbach, *Tetrahedron Lett.*, 2609 (1966); U. S. Patent 3,523,972 (1970); *J. Org. Chem.*, **36**, 777, 2968 (1971).
(19) S. C. Bell, U. S. Patent 3,509,148 (1970).
(20) M. Denzer and H. Ott, *J. Org. Chem.*, **34**, 183 (1969); H. Ott, U. S. Patent 3,531,474 (1970).
(21) G. N. Walker, U. S. Patents 3,560,501 (1971), 3,646,028 (1972); *Chem. Abstr.*, **70**, 106556 (1969); M. H. Sherlock, U. S. Patent 3,466,284 (1969).
(22) S. C. Bell and S. J. Childress, *J. Org. Chem.*, **27**, 1691 (1962).
(23) E. C. Taylor and K. Lenhard, *J. Amer. Chem. Soc.*, **90**, 2424 (1968).
(24) S. C. Bell, C. Gochman, and S. J. Childress, *ibid.*, **28**, 3010 (1963).
(25) S. C. Bell and S. J. Childress, *ibid.*, **29**, 506 (1964).
(26) W. Metlesics, G. Silverman, and L. H. Sternbach, *ibid.*, **29**, 1621 (1964).
(27) S. C. Bell and P. H. L. Wei, *ibid.*, **30**, 3576 (1965).
(28) R. Y. Ning, W. Y. Chen, and L. H. Sternbach, *ibid.*, **36**, 1064 (1971).
(29) A. Walser, G. Silverman, J. Blount, R. I. Fryer, and L. H. Sternbach, *ibid.*, **36**, 1465 (1971).
(30) P. N. Giraldi, A. Fojanesi, G. P. Tosolino, E. Dradi, and W. Logeman, *J. Heterocycl. Chem.*, **7**, 1429 (1970).

SCHEME III



Strecker Nitriles Derived from Secondary *o*-Aminobenzophenones, and Their Conversion to Indoles and Dihydro-5-aryl-2*H*-1,4-benzodiazepines (Scheme III).—Glacial acetic acid again was used in the reaction of the *N*-methylaminobenzophenone **23** with paraformaldehyde and KCN, to give nitrile **24** in good yield. In contrast with **12a**, nitrile **24** did not lose CN^- readily, and was reduced smoothly in the presence of activated nickel catalyst and ammonia. The resulting amino ketone formed the cyclic imine *in situ*, giving the known dihydro-1,4-benzodiazepine **25**, upon which much interest has focused,[31,32] in 75% yield.

Reactions of the relatively stable **24** with various nucleophiles differed from those of labile **12a**. With amines, alkoxides, and other bases, keto aminonitrile **24** underwent facile cyclization to indole **26a** in high yield. Although the keto group of *o*-aminobenzophenones is notoriously unreactive, this internal Claisen reaction apparently is highly favored sterically. Also, when the amino group is tertiary as in **24**, the methylene adjacent to CN may more readily form an anion, and not revert to methyleneiminium + CN^- as it tends to do with an NH present. A rather similar closure of *o*-carbalkoxymethoxy benzophenones with bases to 3-aryl-2-carbalkoxybenzofurans was noted previously.[33]

Cyclization of **24** to **26a** also took place in the presence of dry HCl. The first step in this reaction may be protonation on oxygen, as in vinylogous amides in general; sterically favored nucleophilic attack of methylene on the benzhydrylium ion and dehydration would follow.

With hydroxylamine as the base, there was again facile ring closure, giving the indole amidoxime **26b**, identical with that prepared from **26a** with H_2NOH. The nitrile group in **26a** was found to be inert to electrophilic reagents (HCl, PPA) but quite susceptible to nucleophilic attack and to hydrogenation. Nickel-catalyzed reduction of **26a,b** in the presence of ammonia readily gave the amine **26c**. This compound is identical with one of a number of 2-aminomethyl-3-arylindoles prepared by Japp–Klingemann synthesis from arylhydrazines of 3-aryl-2-carbalkoxyindoles, conversion to 2-carbonitriles, and reduction.[34] Compound **26c** and related 2-aminomethylindoles have in turn been oxidatively opened (O_3 or CrO_3) and the intermediate amino keto amides reclosed to 1,3-dihydro-5-aryl-2*H*-1,4-benzodiazepin-2-ones[34] such as **27**. Thus our investigation of nitriles **12a**, **18a**, and **24** ended with a relay to **27**.

It may be noted that at this point new synthetic routes to four types of known compounds, **4–6**, **15**, **25**, and **27**, of interest in pharmaceutical chemistry, had been found.

Tetracyclic Benzodiazepines and Benzazepines from *o'*-Aminobenzoylbenzoic Acid Derivatives (Scheme IV).—A functional group ortho′ on appended phenyl may be envisioned as potentially useful in conjunction with moieties generated by the ring closures of Scheme III for the synthesis of tetracyclic compounds. Morphanthridine-6,11-diones **28** are prepared by Schmidt and other ring expansions of anthraquinones, and from them a number of 11-hydroxy and 11-amino morphanthridin-6-ones are available.[11,35–39] The well-recognized ring opening of the 6,11-diones to *o'*-aminobenzoylbenzoic acids,[40] and of corresponding 6-on-11-ols to 3-*o'*-aminophenylphthalides,[36,41] has been extended somewhat by Ott[11] to synthesis of certain 1-*o'*-aminophenylisoindolines from 11-aminomorphanthridin-6-ones. The problem in further use of *o'*-aminobenzoyl-

(31) L. H. Sternbach, E. Reeder, and G. A. Archer, *J. Org. Chem.*, **28**, 2456, 3013 (1963); *Arzneim. Forsch.*, **18**, 1542 (1968); U. S. Patent 3,553,199 (1971); L. Tamayo, Spanish Patent 356,713 (1970); *Chem. Abstr.*, **73**, 3946 (1970).

(32) T. S. Sulkowski and S. J. Childress, *J. Org. Chem.*, **28**, 2150 (1963).

(33) G. N. Walker and R. T. Smith, *ibid.*, **36**, 305 (1971). See also M. Oklobdžija, M. Japelj, and T. Fajdiga, *J. Heterocycl. Chem.*, **9**, 161 (1972).

(34) H. Yamamoto, S. Inaba, T. Hirohashi, and K. Ishizumi, *Ber.*, **101**, 4245 (1968); S. Inaba, K. Ishizumi, and H. Yamamoto, *Chem. Pharm. Bull.*, **17**, 1263 (1969); **19**, 263,722 (1971); U. S. Patent 3,557,092 (1971); see also *Chem. Abstr.*, **71**, 124519, 124521 (1969); **74**, 3672, 22904, 88075, 88076, 88081, 88086 (1971). See also M. Oklobdžija, M. Japelj, and T. Fajdiga, *J. Heterocycl. Chem.*, **9**, 161 (1972).

(35) A. E. Drukker and C. I. Judd, *J. Heterocycl. Chem.*, **2**, 276 (1965); **3**, 206 (1966); and references cited therein.

(36) F. Hunziker, F. Künzle, and J. Schmutz, *Helv. Chim. Acta*, **49**, 1433 (1966), and references cited therein.

(37) L. H. Werner, S. Ricca, E. Mohacsi, A. Rossi, and V. P. Arya, *J. Med. Chem.*, **8**, 74 (1965).

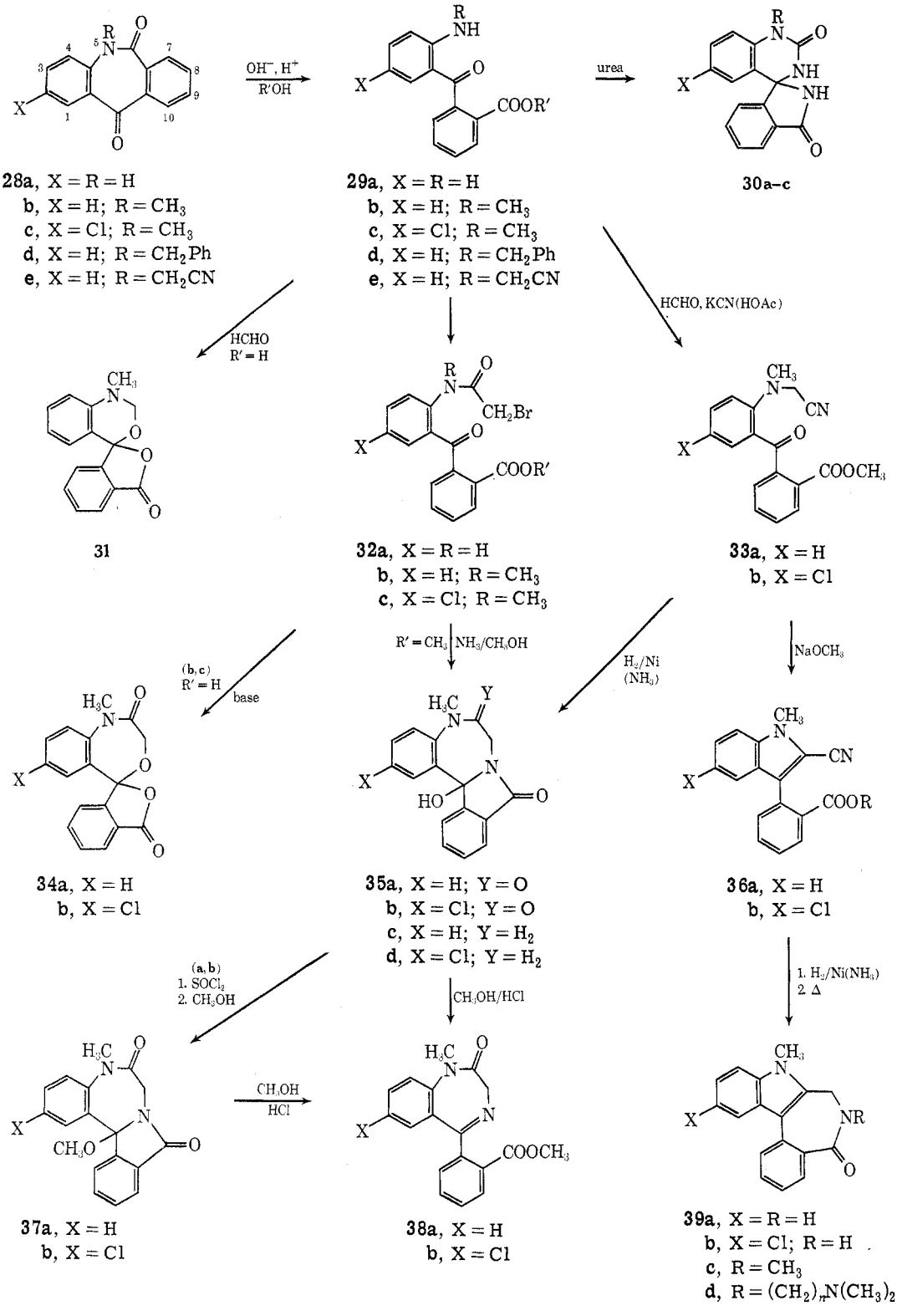
(38) W. S. Waring, U. S. Patent 3,242,167 (1966); *Chem. Abstr.*, **62**, 10422 (1965).

(39) G. N. Walker, U. S. Patents 3,471,473 (1969); 3,504,088, 3,530,219 (1970); 3,632,572, 3,652,550 (1972).

(40) D. D. Emrick and W. E. Truce, *J. Org. Chem.*, **26**, 1329 (1961).

(41) J. O. Jílek, J. Pomykáček, E. Savátek, V. Seidlová, M. Rajšner, K. Pelz, B. Hoch, and M. Protiva, *Collect. Czech. Chem. Commun.*, **30**, 445 (1965).

SCHEME IV



28a, X = R = H
b, X = H; R = CH_3
c, X = Cl; R = CH_3
d, X = H; R = CH_2Ph
e, X = H; R = CH_2CN

29a, X = R = H
b, X = H; R = CH_3
c, X = Cl; R = CH_3
d, X = H; R = CH_2Ph
e, X = H; R = CH_2CN

30a–c

31

32a, X = R = H
b, X = H; R = CH_3
c, X = Cl; R = CH_3

33a, X = H
b, X = Cl

34a, X = H
b, X = Cl

35a, X = H; Y = O
b, X = Cl; Y = O
c, X = H; Y = H_2
d, X = Cl; Y = H_2

36a, X = H
b, X = Cl

37a, X = H
b, X = Cl

38a, X = H
b, X = Cl

39a, X = R = H
b, X = Cl; R = H
c, R = CH_3
d, R = $(CH_2)_nN(CH_3)_2$

benzoic acids lies in preventing their relatively facile reclosure to morphanthridin-6-ones.

We found a very useful and apparently not previously suspected fact: ring-opened amino acids **29** (R′ = H) are esterified almost quantitatively on standing with a large excess of methanolic HCl, giving amino keto esters **29** (R′ = CH_3). This provided an opening for new work in the field, albeit esters **29** on fusion with urea give the same type of spiro compounds **30** as have been obtained from **28** with urea.[42]

With HCHO (in attempted Strecker reactions) the acid **29b** (R′ = H) gave spiro compound **31** through reaction of the *N*-methylol with the *o*-benzoylbenzoic acid moiety, whereas the Strecker reaction (in HOAc)

(42) S. Palazzo, *Gazz. Chim. Ital.*, **96**, 1641 (1966); *Chem. Abstr.*, **67**, 32673 (1967).

on corresponding esters **29** (R′ = CH_3) gave desired amino keto ester nitriles **33**. Related findings were made with bromoacetyl acids and esters **32** (R′ = H and CH_3, respectively). On attempting to displace Br with NH_3 or other amines in **32** (R′ = H), the ring tautomeric carboxylate ion apparently functioned as the nucleophile, resulting in formation of novel spiro compounds **34**. However, the Br was replaced normally with NH_3 in methanol[43] in esters **32** (R′ = CH_3), and interaction of the side chain NH_2 group with the keto ester led as expected[44] to the tetracyclic hydroxyphthalimidines **35a,b**. Similarly, nickel-catalyzed reduction of nitriles **33**, in the presence of NH_3, generated an amino group which interacted with the keto ester moiety in the same way, giving **35c,d**, albeit in rather low yields.

Compounds **35**, novel inasmuch as isoindolo[2,1-*d*]-[1,4]benzodiazepines at so high a level of oxidation had not been synthesized previously, underwent some quite interesting transformations. With warm, methanolic HCl, **35a** was solvolytically ring opened and dehydrated to the *o*′-carbomethoxy-2*H*-1,4-benzodiazepin-2-one **38a**, a type of compound previously mentioned in passing but not actually prepared.[45] The acid imine hydrochloride corresponding to **38a** was obtained by treatment of **35a** with dry HCl in the absence of methanol. Performing similar operations on the 2-chloro analog **35b**, one learned that the 13b position is influenced electronically by the 2-chloro substituent in a more or less predictable sense (*i.e.*, vinylogously similar to an α-chloro C=O moiety). On short exposure to warm MeOH–HCl, **35b** gave the 13b-methoxy compound **37b**, and on longer exposure to the same reagent either **37b** or **35b** afforded **38b**. Formation of 3-alkoxyphthalimidines under rather different circumstances has been observed previously.[44] The des-2-chloro-13b-methoxy compound **37a** was not obtained similarly, but was prepared by treatment of **35a** with thionyl chloride and then methanol.[44]

To obtain compounds corresponding to **35a,b** with NH in place of the *N*-methyl group at position 5, it was planned originally to proceed *via* **32** with R = benzyl; therefore **28d** and **29d** (R′ = H and CH_3) were prepared. Later, however, **32a** (R′ = CH_3) from bromoacetylation of **29a** (R′ = CH_3) was found to give **35a** (H in place of CH_3) directly with NH_3 in methanol.

Secondary aminonitriles **29e** (R′ = H and CH_3) were obtained by carefully opening **28e** to a potassium salt, followed by acidification or methylation (CH_3I); however, neither these nor **28e** itself gave recognizable products on nickel reduction, and like the compounds of Scheme II were not converted into indoles.

Strecker nitriles **33**, like **24**, were converted by $NaOCH_3$ in methanol to indoles **36**, with accompanying solvolysis to corresponding acids (R = H), a fact which speaks for the probable intervention of lactonic (ring tautomeric carboxylate) derivatives of intermediate ketols. Acids **36** having been reesterified to corresponding esters **36** (R = CH_3), hydrogenation in the presence of nickel and NH_3 was found to give (as with **26a** → **26c**) corresponding 2-aminomethylindoles. These were closed readily to lactams **39a,b**, which represent a ring system not previously synthesized, the indolo[2,3*d*][2]benzazepines, and which, like other 2-benzazepin-1-ones,[46] are alkylated by usual techniques, *e.g.*, to **39c,d**.

Hydride Reductions and Hydrogenolyses in Isoindolo-[2,1-*d*][1,4]benzodiazepines.—In our earlier work[12] lithium aluminum hydride reduction of **8a** (Scheme I) was found to be anomalous, giving mainly **9a**. We find that reaction of **8b** with $LiAlH_4$ similarly gives almost exclusively the fused hydroxyphthalimidine **9b**, rather than the cyclic tertiary amine. Presumably these reactions proceed to fused isoindoles, which undergo autooxidation during work-up, leading to **9**. In the light of this information, it was rather surprising to find that compounds **4**, with a basic rather than a neutral atom at position 5, are reduced normally with $LiAlH_4$ to the fused isoindolines **5**.

This difference may be explained by assuming that, in **4**, it is (vinylogously) as though nitrogen atom 5 were attached directly to position 13b, electronically inhibiting the loss of proton 13b along with 9-hydroxy of a presumed, intermediate carbinolamine to form an isoindole.

In synthesizing 6,7-dihydro-13b*H*-isoindolo[2,1-*d*]-[1,4]benzodiazepin-6-ones and the 6,9-diones by a different approach, Hardtmann and Ott[11] evidently encountered *de novo* the anomalies long known to attend the preparation of 1-phenylisoindolines by reduction of phthalimidines, and were obliged to resort to electrolytic reduction of phthalimidines or Zn/HOAc reduction of isoindoles in preparation of their intermediate isoindolines. It is also relevant to note that they did not report any $LiAlH_4$ reductions of their 6-oxo analogs of **4**. We find similarly that compounds **35** (Scheme IV) cannot be reduced with $LiAlH_4$ to recognizable products.

On the other hand, acid-catalyzed hydrogenolysis (Pd) of 5-benzyl and 13b-hydroxy groups in compounds such as **4** and **35** proceeds normally. Thus **4d** HCl was converted to **6**. Hydroxy lactams **35a,c**, as well as 5-desmethyl **35a**, were hydrogenolyzed with Pd/C in warm HOAc to give corresponding 13b-desoxy lactams. The hydrogenolysis of **35c** gave **4a**, identical with that prepared by cyclization of **3a**, providing a welcome confirmation of structures of tetracyclic lactams prepared by quite different routes.

Experimental Section

Melting points (uncorrected) were obtained using a Thomas-Hoover silicone oil bath; ir spectra (Nujol mulls unless otherwise noted) were taken on a Perkin-Elmer 21 double beam instrument; uv curves (MeOH solutions) were measured with a Cary 14 recording spectrophotometer; mass spectra were recorded using a MS-902 double-focusing apparatus; nmr spectra were obtained with a Varian A-60, Me_4Si internal standard.

***N*-Methylanilinoacetonitrile (1a).**—To a solution of 110 g (1.06 mol) of sodium bisulfite in 300 ml of water was added 36% formalin (88 g, 1.06 mol), and 10 min later there was added 106 g (1.00 mol) of *N*-methylaniline. The mixture was heated on a steam cone and stirred vigorously for 0.8 hr; the hot solution

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(44) W. Graf, E. Girod, E. Schmidt, and W. G. Stoll, *Helv. Chim. Acta*, **42**, 1085 (1959), and references cited therein.

(45) E. Reeder and L. H. Sternbach, U. S. Patent 3,109,843 (1963).

(46) G. N. Walker and D. Alkalay, *J. Org. Chem.*, **36**, 461 (1971).

was treated with a concentrated aqueous solution of 65 g (1.00 mol) of KCN and heated for 0.5 hr longer. After cooling, the oil was extracted with ether. The washed (water, two portions) and dried (K_2CO_3) ether solution was evaporated and the crude oil (136 g) was distilled *in vacuo* to give 109 g (75%) of oil, bp 86–91° (0.4–0.5 mm) [lit.[8] bp 105–110° (2 mm)], ir 4.48 μ (very weak).

Nitriles **1b** and **1c** were prepared by a similar Knoevenagel–Bucherer–modified Strecker technique,[7] from appropriate precursor *N*-methylanilines, as follows.

Nitrile 1b. A.—N-Methylation of 113 g of *p*-chloroacetanilide (mp 178°; prepared from *p*-chloroaniline with Ac_2O) with excess CH_3I (100 ml) in the presence of NaH (30 g, 56%) in DMF (700 ml), evaporation on a steam cone (1 hr), treatment with water, and extraction with ether gave 78 g (63%) of *N*-methyl-*p*-chloroacetanilide, mp 78–84°.[47]

B.—Hydrolysis of 75 g of the acetyl derivative (A) with 40 g of NaOH ln 175 ml of water and 200 ml of ethanol (6 hr reflux) and isolation of the amine by extraction with 15% HCl and treatment with NaOH solution, gave 50 g of *p*-chloro-*N*-methylaniline as an oil.

C. Strecker Reaction.—Sodium bisulfite solution (47 g, 0.45 mol, in 300 ml of water) and 36% formalin (38 g, 0.45 mol) were combined, crude *p*-chloro-*N*-methylaniline (50 g, 0.35 mol) was added, the suspension was stirred at 90° for 1.5 hr, and the aqueous solution was decanted from residual brown oil and treated with a concentrated aqueous solution of 32 g (0.49 mol) of KCN. After heating at 70–80° for 0.5 hr, the cooled suspension was extracted with ether, and the ether solution was washed with water, dried (K_2CO_3), and evaporated, yielding 35 g (51%) of **1b** as an oil, 88% pure by gpc, ir 4.46 μ (barely discernible).

The nitrile was characterized by preparation of the corresponding amidoxime dihydrochloride, as follows. To a solution of 0.7 g of Na in 250 ml of ethanol was added 2.1 g of $H_2NOH \cdot HCl$ and 5.35 g of nitrile. After refluxing for 1 hr, the filtered, evaporated, and refiltered ethanol solution of base was treated with dry HCl to give colorless crystals: mp 195–196° (from EtOH); ir 2.93, 3.16, 5.95, and 6.28 μ; uv 252 nm (ε 18,210) and 300 (1860); $FeCl_3$ test, deep red.

Anal. Calcd for $C_9H_{12}ClN_3O \cdot 2HCl$: C, 43.22; H, 5.24; N, 16.80. Found: C, 43.06; H, 5.24; N, 16.44.

Nitrile 1c. A.—N-Methylation of 114 g of *m*-methoxyacetanilide[48] with CH_3I in the presence of 34 g of 56% NaH in DMF gave 46 g of *N*-methyl-*m*-methoxyacetanilide: mp 67–68° (from ligroin); ir 6.03 μ; uv 274 nm (ε 2380) and 281 (2190).

Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 67.39; H, 7.48; N, 7.89.

B.—Hydrolysis of 40 g of material from A with 40 g of NaOH in 300 ml of aqueous EtOH (4 hr reflux), dilution and extraction with ether, reextraction with dilute HCl, and regeneration of the base (NaOH) afforded 29 g of crude *m*-methoxy-*N*-methylaniline as a purplish oil, suitable for further work: ir 2.94 μ; uv 207 nm (ε 32300), 246 (9060), and 290 (2590).

C. Strecker Reaction.—Combining 28.5 g of $NaHSO_3$ in 200 ml of water with 25 ml of formalin (36%), then adding crude amine from B and warming on a steam cone for 1 hr with stirring, resulted in solution of nearly all the material. The warm solution was filtered clear, diluted with 200 ml of water, treated with 22 g of KCN, and heated gently on a steam cone for 20 min. The oily product, after cooling, was extracted with ether, and the ether solution was washed three times with water, dried over K_2CO_3, and evaporated to give 21.5 g of crude **1c**: ir virtually devoid of NH peak, CN band barely visible; uv 210 nm (ε 33,740), 246 (9910), and 286 (2650). The material was suitable for use without purification.

***p*-Chloroanilinoacetonitrile.**—Following the literature procedure,[7] using 0.53 mol each of $NaHSO_3$ and HCHO and 64 g (0.50 mol) of *p*-chloroaniline in 500 ml of water, heating on a steam cone, and stirring for 0.6 hr, there was obtained 0.50 mol of $p\text{-}ClC_6H_4NHCH_2SO_3^-Na^+$, which is sparingly soluble in water and crystallizes from the aqueous solution on cooling: mp *ca.* 265° dec; ir 2.81, 2.93, 6.12, and 6.27 μ. The solution was diluted with 500 ml of additional water, reheated, treated with an aqueous solution of 42 g of KCN, and heated on a steam cone, for 1.5 hr. The product crystallized on cooling and was collected washed with water, and air dried: yield 48 g of crystals; mp 57–63° (95% pure by gpc), raised on recrystallization from ether–ligroin to mp 66–67.5° (lit.[7] mp 66.5–68°); ir 2.95 (strong) and 4.45 μ (very weak); uv 246 nm (ε 16,630) and 298 (1840).

Anal. Calcd for $C_8H_7ClN_2$: C, 57.66; H, 4.24; N, 16.82. Found: C, 57.33; H, 4.41; N, 16.60.

Additional material, obtained on addition of more KCN and further (4 hr) heating of the aqueous solution remaining from the foregoing reaction, proved not to be more nitrile, but rather a by-product, *p*-chloroanilinoacetamide: crystals from ether; mp 129–131°; ir 2.94, 3.03, 3.17, 5.98, and 6.08 μ; uv 249 nm (ε 16,920) and 302 (1900).

Anal. Calcd for $C_8H_9ClN_2O$: C, 52.04; H, 4.91; N, 15.18. Found: C, 52.11; H, 5.29; N, 14.85.

The *N*-acetyl derivative of the aminonitrile was prepared by heating a sample with excess Ac_2O at 100° or reflux (1 hr): colorless crystals from ether; mp 72–73°; ir 4.47 (very weak) and 5.99 μ; uv 224 nm (ε 10,760) and 260 (330).

Anal. Calcd for $C_{10}H_9ClN_2O$: C, 57.56; H, 4.35; N, 13.43. Found: C, 57.72; H, 4.35; N, 13.30.

The *p*-chloro-*N*-acetylanilinoacetonitrile (5.6 g) was also converted to the corresponding amidoxime by 1-hr reflux in an ethanolic (250 ml) solution of hydroxylamine (prepared using 0.6 g of Na and 1.85 g of $H_2NOH \cdot HCl$): yield 5.2 g of crystals from EtOH; mp 175–177°; ir 2.89, 2.98, 3.12, 6.00, and 6.14 μ; uv inflection 220 nm (ε 13,170); $FeCl_3$ test deep red or green.

Anal. Calcd for $C_{10}H_{12}ClN_3O_2$: C, 49.69; H, 5.01; N, 17.39. Found: C, 49.44; H, 4.93; N, 17.03.

***N*-Benzylanilinoacetonitrile (1d).**—Glacial acetic acid (200 ml) was added with stirring to a mixture of 26.8 g (0.146 mol) of *N*-benzylaniline, 9 g (0.30 mol) of paraformaldehyde, and 19.5 g (0.30 mol) of KCN. The materials dissolved in *ca.* 10 min, the temperature rising to *ca.* 50°. After stirring for 2 hr, the solution was added to 1.2 l. of water and the resulting oil was extracted with ether. The washed ($NaHCO_3$ solution, water) and dried (K_2CO_3) ether solution was evaporated, and the oil was distilled *in vacuo:* 11.2 g (35%); bp 141–145° (0.3 mm); 94% pure by gpc; ir nearly devoid of NH, 4.48 μ (barely visible).

***N*-Benzyl-4-veratrylaminoacetonitrile (1e)** was obtained by similar Dimroth-modified Strecker reaction from a suitable precursor prepared as follows.

A. 4-*N*-Benzylideneveratrole.—A solution of 15.3 g of 4-aminoveratrole and 11 g of benzaldehyde in 200 ml of benzene was refluxed under a water trap for 1.5 hr and evaporated to give 25 g of crude, crystalline imine: mp 54–55° after recrystallization from cyclohexane; ir 6.18–6.28 μ; uv 256 nm (ε 18,910) and 339 (12,230).

Anal. Calcd for $C_{15}H_{15}NO_2$: C, 74.66; H, 6.26; N, 5.81. Found: C, 74.90; H, 6.35; N, 5.70.

B.—$NaBH_4$ was added in excess to 25 g of imine (A) in methanol (200 ml) and after 2 hr the MeOH was evaporated, the residue was treated with water, and the product was extracted with ether; the water-washed and dried (K_2CO_3) solution gave on evaporation 23 g of crude 4-*N*-benzylveratrole as an oil.

C. Strecker Reaction.—To a mixture of 22.6 g (0.093 mol) of amine from B, 8.4 g (0.28 mol) of paraformaldehyde, and 18.2 g (0.28 mol) of KCN was added 140 ml of glacial acetic acid, and the suspension was warmed to 50–60° periodically (four or five times) while stirring, over the course of 4.5 hr. The cooled solution was diluted with 1 l. of water, and the oil was extracted with ether–ethyl acetate, washed with 5% $NaHCO_3$ solution and water, dried (K_2CO_3), and evaporated to give 26 g of crude crystals yielding on trituration with ether 19 g of product, mp 81–84°. Recrystallization from ether gave colorless crystals: mp 86–87°; ir 6.20–6.25 μ (CN peak scarcely visible); uv 207 nm (ε 37,130), 245 (11,270), and 294 (3110).

Anal. Calcd for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92. Found: C, 72.30; H, 6.33; N, 10.05.

A sample (4.2 g) of the nitrile was converted by 2-hr reflux with 170 ml of ethanolic H_2NOH (from 0.95 g of Na and 2.8 g of $H_2NOH \cdot HCl$) to the corresponding amidoxime (3 g). Recrystallization from aqueous ethanol, then benzene, gave, as the hydrate, colorless crystals: mp 91–96°; ir 2.91, 3.01, and 6.01 μ; uv 249 nm (ε 12,150) and 303 (4460); $FeCl_3$ test red.

Anal. Calcd for $C_{17}H_{21}N_3O_3 \cdot H_2O$: C, 61.24; H, 6.95; N, 12.61. Found: C, 60.80; H, 6.90; N, 12.38.

Hydrogenation of Nitriles 1 to *N*-(2-Aminoethyl)anilines 2.—The reduction procedure may be exemplified by preparation of *N*-(2-aminoethyl)-*N*-methylaniline (**2a**). To 250 ml of ethanol saturated with NH_3 at room temperature was added 27.6 g

(47) *Cf.* R. Stoermer and P. Hoffmann, *Ber.*, **31**, 2523 (1898); F. D. Chattaway and K. J. P. Orton, *J. Chem. Soc.*, **79**, 461 (1901).

(48) F. Reverdin and A. de Luc, *Ber.*, **47**, 1537 (1914).

(0.19 mol) of nitrile **1a** and 1–2 parts by weight of moist, water- and alcohol-washed W. R. Grace 28 activated nickel catalyst. The suspension was shaken under hydrogen at 45–50 lb initial gauge pressure (Parr apparatus; 4-l. reserve tank) at room temperature for 5 hr. A pressure drop of 30 lb gauge, nearly complete in 3 hr, indicated uptake of $2H_2$. The catalyst was filtered and the solution was evaporated to give 26.7 g of diamine as a pale yellow oil, sufficiently pure for further work, ir 2.98–3.0 μ.

It was found to be preferable to distil nitrile **1a** and use crude diamine **2a** as obtained directly from the reduction, rather than attempt to purify **2a** by distillation, as serious losses resulted in the latter procedure; in one run, crude **2a** (80% pure by gpc) from apparently complete reduction of 132.7 g of crude nitrile **1a** on distillation gave only 68.1 g (50% overall yield) of **2a**, bp 62–66° (0.1–0.3 mm) [lit.[8] bp 94–97° (2 mm)].

A sample of the corresponding dihydrochloride was prepared as colorless crystals (from methanol), mp 205–208° dec, ir 4.09 μ (very broad).

Anal. Calcd for $C_9H_{14}N_2 \cdot 2HCl$: C, 48.44; H, 7.23; N, 12.56. Found: C, 48.80; H, 7.37; N, 12.45.

Diamines **2b–e** were prepared from corresponding precursors **1** by the same procedure. Occasionally it was necessary to recharge with fresh catalyst in order to achieve smooth reduction (**2b,c**) of crude nitriles, and in some instances (**2c,e**) the crude diamine was taken into ether, washed with water, and dried (K_2CO_3) and the solvent was reevaporated, in order to obtain materials suitable for further work.

Compound 2b (90% pure by gpc) was characterized as the corresponding hydrochloride: crystals from EtOH, mp 252–255° dec; uv 257 nm (ϵ 19,260) and 306 (1840).

Anal. Calcd for $C_9H_{13}ClN_2 \cdot HCl$: C, 48.88; H, 6.38; N, 12.67. Found: C, 48.79; H, 6.41; N, 12.88.

Compound 2c was an oil: ir broad NH_2 band; uv 211 nm (ϵ 29,690), 251 (11,580), and 294 (2910). Like **2c** it formed a dihydrochloride as crystals (from EtOH): mp 178–181° dec; uv 211 nm (ϵ 32,380), 248 (12,060), and 290 (2930). Exact analytical figures could not be obtained. Similar results were observed with **2d** 2HCl.

Compound 2e was characterized as the dihydrochloride: crystals from ethanol–ether; mp 194–196° dec; ir 4.31 μ (broad, with side bands); uv 249 nm (ϵ 10,240) and 302 (2800).

Anal. Calcd for $C_{17}H_{22}N_2O_2 \cdot 2HCl$: C, 56.83; H, 6.73; N, 7.80. Found: C, 56.74; H, 6.80; N, 7.45.

2-(3-Phthalidylamino)ethylanilines 3.—Each of these intermediates was prepared by a facile azeotropic condensation: a solution of 0.1 mol each of the appropriate arylalkylaminoethylamine **2** and *o*-carboxybenzaldehyde in 150–200 ml of benzene was refluxed under a water separator for 1–2 hr, an amount of water corresponding closely to theory being trapped. Evaporation of the resulting solutions gave viscous oil in each case, having a strong ir 5.7-μ peak and frequently a weaker 5.91-μ band. The crude products were used *per se* in cyclizations, without undue delay. Some of the materials, notably crude **1a** and **1b**, tended to crystallize partly on standing; it was futile to attempt fractionation, as amall crystalline fractions isolated by various triturations on several occasions proved not to be samples of compounds **3** but rather impure samples of by-products.

5-Methyl-6,7-dihydroisoindolo[2,1-*d*][1,4]benzodiazepin-9-(13b*H*)-one (4a).—Cyclization of compounds **3** to tetracyclic lactams **4** was carried out typically as follows. A mixture of 20 g of crude **3a** and 300 g of PPA was stirred and heated in a steam bath for 0.7 hr. The resulting deep green solution was cooled and added with stirring to 1600 ml of ice–water. In the case of **4a** it was necessary to convert the H_3PO_4 solution to a buffered medium by addition of cold, aqueous NaOH to bring about complete separation of crude product; in the remaining examples **4b–e** this was not necessary. The crude material was collected (**4a,d,e**) or extracted with ether (**4b,c**), and washed with water. An ether, ether–ethyl acetate, or benzene solution of the crude material was washed with successive portions of 2% NaOH solution and water, dried (Na_2SO_4), and evaporated. Trituration of the semicrystalline residue afforded 6.8 g (36%) of **4a** as crystals, mp 143–148°. Recrystallization from ether and methanol gave a pure sample: mp 145–148°; ir 5.92 μ; uv 250 nm (ϵ 12,640) and 280 (4230); nmr ($CDCl_3$) δ 8.1–6.9 (m, 8, ArH), 5.9 (s, 1, methine), 3.2–4.1 (m, 4, methylenes), and 2.98 (s, 3, NCH_3).

Anal. Calcd for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10; N, 10.60. Found: C, 77.41; H, 6.26; N, 10.56.

Compound 4b was obtained from similar cyclization of **3b** in 34% yield: crystals (from ether); mp 140–141°; ir 5.88–5.93 μ; uv 257 nm (ϵ 13,180) and inflection 300 (2480); nmr ($CDCl_3$) δ 8.2–6.9 (m, 7, ArH), 5.88 (s, 1, methine), 3.2–4.1 (m, 4, methylenes), and 2.98 (s, 3, NCH_3).

Anal. Calcd for $C_{17}H_{15}ClN_2O$: C, 68.34; H, 5.06; N, 9.38. Found: C, 68.41; H, 5.39; N, 9.35.

Compound 4c was obtained from **3c** in 27% yield: crystals (from methanol); mp 132–134°; ir 5.95 μ; uv 220 nm (ϵ 37,820), inflection 248 (13,190), 279 (4400), and inflection 291 (2870); nmr ($CDCl_3$) δ 7.96 (q, 1, proton 10), 7.7–7.4 (m, 3, protons 11, 12, and 13), 6.88 (d, 1, J = 8 Hz, proton 1), 6.67 (d, 1, J = 2.2 Hz, proton 4), 6.43 (q, 1, J_{ortho} = 8 J_{meta} = 2.2 Hz, proton 2), 5.84 (s, 1, methine), 4.2–3.2 (m, 4, methylenes), 3.8 (s, 3, OCH_3), and 2.96 (s, 3, NCH).

Anal. Calcd for $C_{18}N_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.76; H, 6.33; N, 9.53.

Compound 4d was obtained from **3d** with PPA after 1.5 hr: yield 65%; initially obtained crystalline by tlc; crystals from ether; mp 116–119°; ir 5.89 μ; uv 249 nm (ϵ 13,120) with inflection at 228 (15,580) and 280 (4460); nmr ($CDCl_3$) δ 8.1–6.8 (m, 13, ArH), 6.0 (s, 1, methine), 4.44 (q, 2, J_{AB} = 14 Hz, benzyl CH_2), 3.8–2.8 (m, 4, methylenes).

Anal. Calcd for $C_{23}H_{20}N_2O$: C, 81.15; H, 5.92; N, 8.23. Found: C, 80.86; H, 6.05; N, 8.12.

Compound 4e was obtained from **3e** with PPA after 0.5 hr: yield 43%; crystals from ethanol; mp 157–158°; ir 5.93 μ; uv 250 nm (ϵ 14,950), inflection at 279 (4680), and 297 (4460); nmr ($CDCl_3$) δ 7.94 (q, 1, proton 10), 7.7–7.2 (m, 8, C_6H_5 and protons 11, 12, and 13), 6.77 (s, 1, proton 1), 6.55 (s, 1, proton 4), 6.0 (s, 1, methine), 4.42 (q, 2, J_{AB} = 13 Hz, benzyl CH_2), 4.0–2.8 (m, 4, methylenes), with 3.88 (s, 3, OCH_3) and 3.64 (s, 3, OCH_3).

Anal. Calcd for $C_{25}H_{24}N_2O_3$: C, 74.98; H, 6.04; N, 7.00. Found: C, 75.18; H, 6.00; N, 7.12.

5-Methyl-6,7,9,13b-tetrahydroisoindolo[2,1-*d*][1,4]benzodiazepine (5a).—Reduction of 3.5 g of lactam **4a** with a stirred, refluxing solution of 3.5 g of $LiAlH_4$ in 290 ml of ether and 25 ml of THF for 3.5 hr, followed by treatment with water (17.5 ml, stirred 1 hr), filtration, and evaporation of the dried (K_2CO_3) solution, gave 2.1 g (63%) of amine as crystals from ether, mp *ca.* 95–100°. A sample, recrystallized from methanol and dried *in vacuo* at 75°, had mp 85–88°; ir 3.53 (weak) and 6.25 μ; uv 254 nm (ϵ 6940), 271 (3790), and inflection at 286 (1950); nmr ($CDCl_3$) δ 7.4–6.8 (m, 8, ArH), 5.56 (s, 1, methine), 4.02 (s, 2, methylene position 9), and 3.6–2.6 (m, 4, methylenes) with 2.9 (s, 3, NCH_3).

Anal. Calcd for $C_{17}H_{18}N_2$: C, 81.56; H, 7.25; N, 11.19. Found: C, 81.54; H, 7.07; N, 11.37.

The corresponding hydrochloride was recrystallized from ethanol–ether as colorless crystals: mp 180–183° dec; ir 4.57 μ (intense, broad); uv 251 nm (ϵ 6500), inflection at 270 (3150) and 276–290 (2040).

Anal. Calcd for $C_{17}H_{18}N_2 \cdot HCl$: C, 71.19; H, 6.68; N, 9.77. Found: C, 71.78; H, 6.69; N, 9.85.

Compound 5b, prepared by similar $LiAlH_4$ reduction of **4b**, crystallized in ether–ligroin and was recrystallized from methanol: crystals; mp 109–110.5°; ir 3.64 (weak) and 6.28 μ; uv 262 nm (ϵ 9320) and inflections at 272 (7130), 300 (1970); nmr ($CDCl_3$) δ 7.4–6.8 (m, 7, ArH), 5.53 (s, 1, methine), 4.06 (s, 2, methylene at position 9), and 3.6–2.6 (m, 4, methylenes) with 2.9 (s, 3, NCH_3).

Anal. Calcd for $C_{17}H_{17}ClN_2$: C, 71.69; H, 6.02; N, 9.84. Found: C, 71.49; H, 6.27; N, 9.90.

The corresponding hydrochloride, recrystallized from ethanol–ether, had mp 248–250° dec; ir 4.54 (intense, broad); uv 258 nm (ϵ 9270) and 298 (2100).

Anal. Calcd for $C_{17}H_{17}ClN_2 \cdot HCl$: C, 63.56; H, 5.65; N, 8.72. Found: C, 63.40; H, 5.81; N, 8.66.

Compound 5c, from similar reduction of **4c**, did not crystallize, and was characterized by preparation of the corresponding hydrochloride: slightly unstable and discolored crystals; mp 231–233° dec (from ethanol–ether); ir 4.36–4.44 μ (strong); uv 222 nm (ϵ 32,650), 252 (6520), and inflections at 270 (3520) and 288 (1930).

Anal. Calcd for $C_{18}H_{20}N_2O \cdot HCl$: C, 68.23; H, 6.68; N, 8.84. Found: C, 68.53, 68.06; H, 6.64; N, 8.74.

Compound 5e, from **4e**, in the course of isolation was converted with 10% hydrochloric acid to the corresponding, water-insoluble hydrochloride, which was recrystallized from ethanol (Norit) and a small amount of ether: slightly lavender crystals; mp 225–227°

dec; ir 4.42 μ (intense); uv 256 nm (ε 9960) and 297 (4070) with inflection at 269 (5430).

Anal. Calcd for $C_{25}H_{26}N_2O_2 \cdot HCl$: C, 70.99; H, 6.44; N, 6.62. Found: C, 71.31; H, 6.65; N, 6.59.

6,7-Dihydroisoindolo[2,1-*d*][1,4]benzodiazepin-9(5*H*,13b*H*)-one (6).—To a solution of 3.6 g of **4d** in 200 ml of glacial acetic acid containing *ca.* 3 g of dry HCl was added 0.5 g of 10% Pd/C, and the suspension was shaken under 45 lb of H_2 at 50° for 6.5 hr. Evaporation of the filtered solution and trituration of the residue with ether gave 3.0 g of the hydrochloride as crystals (from ethanol): mp 253–256° dec; ir 3.79 (broad) and 5.84 μ; uv 240 nm (ε 11,950) and 279 (2950) with inflection at 227 (14,490).

Anal. Calcd for $C_{16}H_{14}N_2O \cdot HCl$: C, 67.01; H, 5.27; N, 9.77. Found: C, 67.22; H, 5.35; N, 9.42.

The corresponding base, from treatment of the hydrochloride in methanol with 10% NaOH solution, extraction with benzene, and recrystallization from ether–benzene, had mp 135–137°; ir 3.00 and 5.96 μ; uv 241 nm (ε 12,020) and 279 (3450) with inflection at 228 (14,630); nmr ($CDCl_3$) δ 8.0–6.7 (m, 9, ArH and NH), 5.72 (s, 1, methine), and 4.5–3.3 (m, 4, methylenes).

Anal. Calcd for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.19. Found: C, 76.95; H, 6.04; N, 10.92.

2,3-Dimethoxy-6,7,9,13b-tetrahydroisoindolo[2,1-*d*][1,4]benzodiazepine Hydrochloride.—A solution of 1.3 g of **5e** in 200 ml of ethanol and 1 ml of 5% ethanolic HCl, containing 0.5 g of 10% Pd/C, was shaken under 45 lb of H_2 at 60° for 8 hr, cooled, and filtered, and the solvent was evaporated, The crude salt with dilute NaOH gave an oily base which, after ether–benzene extraction, drying (K_2CO_3), and evaporation, was reconverted to hydrochloride, 0.6 g of gray crystals, mp *ca.* 217° dec, purified by recrystallization from ethanol: colorless crystals: mp 244–246° dec (after drying *in vacuo* at 80°); ir 3.09 (moderate to intense, sharp), and 4.05–4.11 μ (intense); uv 210 nm (ε 47,100), 248 (10,540), 270 (2310), and 297 (5140).

Anal. Calcd for $C_{18}H_{20}N_2O_2 \cdot HCl$: C, 64.95; H, 6.36; N, 8.42. Found: C, 65.13; H, 6.50; N, 8.46.

5,6-Dihydroisoindolo[1,2-*a*][2]benzazepin-9(7*H*,13b*H*)-one (8b). **A.**—Crude 3-(γ-phenylpropylamino)phthalide (**7b**) was prepared by 1-hr reflux of a solution of 25 g of γ-phenylpropylamine and 26.8 g of phthalaldehydic acid in 250 ml of benzene under water separator, and evaporation of the solvent: viscous, semicrystalline oil, ir 5.71 μ.

B.—Cyclization of 30 g of crude A with 200 g of PPA at 95° for 1.5 hr, hydrolysis of the cooled, light brown solution with 1 l. of ice–water, and extraction with ether gave after evaporation of the washed and dried ether solution 8.5 g (30%) of crystals, mp 140–145° from ether, raised to 143–145° on recrystallization from ethanol: ir 5.91 μ; uv 249 nm (ε 5210) and inflections at 270 (3340) and 279 (1890); nmr ($CDCl_3$) δ 7.9 (q, 1, proton 10), 7.6–7.0 (m, 7, ArH), 5.74 (s, 1, methine), 4.38 (octet, 1, probably proton 7_{eq}), 3.4 (m, 1, probably proton 7_{ax}), 2.73 (m, 2, methylene position 5), and 2.4–1.7 (m, 2, methylene position 6).

Anal. Calcd for $C_{17}H_{15}NO$: C, 81.90; H, 6.06; N, 5.62. Found: C, 82.15; H, 6.17; N, 5.79.

13b-Hydroxy-5,6-dihydroisoindolo[1,2-*a*][2]benzazepin-9(7*H*,13b*H*)-one (9b).—A solution of 5.2 g of **8b** in 50 ml of THF was added (10 min) to $LiAlH_4$ (4 g) in 200 ml of THF with stirring, and the suspension was refluxed and stirred for 2 hr. There was initially a green color, later becoming orange-brown. The cooled mixture was diluted with ether, treated with 20 ml of water cautiously, stirred for 1 hr, and filtered. Evaporation of the dried (K_2CO_3), yellow filtrate gave *ca.* 4.5 g of crude crystals. Basic material (1.4 g of brown, unstable oil) was removed by extraction with dilute HCl, and the washed ($NaHCO_3$, H_2O) and dried ether solution of neutral material was evaporated, to give 3 g of crude crystals, mp *ca.* 200°, purified by tlc and recrystallization from ethanol to give colorless crystals: mp 230–233° dec; ir 3.19 and 5.97 μ; uv 256 nm (ε 3880) and inflection 265 (3360); nmr (DMSO) similar to that of **8b** in complexity, methine absent, and δ 6.9 (s, 1, exchanges with D_2O, OH).

Anal. Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 77.07; H, 5.73; N, 4.95.

Bis(2-benzoyl-4-chloroanilino)methane (11).—A solution of 15 g of 2-amino-5-chlorobenzophenone in 125 ml of glacial HOAc was treated with 6.3 g of paraformaldehyde and warmed on a steam cone for 1 hr. The cooled suspension of yellow crystals was filtered, and, after washing with water and drying, the crude product was recrystallized from ethyl acetate as yellow crystals: mp 184.5–186°; ir 3.05 (weak), 6.13, and 6.34 μ; uv 236 nm (ε 27,250) and 387 (6210); nmr ($CDCl_3$) δ 8.8 (t, 2, slow D_2O exchange, NH), 7.6–6.7 (m, 16, ArH), and 4.77 (t, 2, J = 6 Hz, methylene); mass spectrum m/e 231 and 243.

Anal. Calcd for $C_{27}H_{20}Cl_2N_2O_2$: C, 68.22; H, 4.24; N, 5.89. Found: C, 68.43; H, 4.12; N, 5.79.

The compound is readily distinguished from **12a** by spectra and the fact that with 18% aqueous HCl it does not develop a red color.

Compound **11** was also obtained by (a) treatment of **12a** (2.9 g) with warm, ethanolic NH_3 (700 ml) for several hours, (b) treatment of **12a** with aqueous, ethanolic NaOH solution, and (c) by treating **12a** with a warm buffered aqueous, alcoholic solution of hydroxylamine.

2-*N*-(Cyanomethyl)amino-5-chlorobenzophenone (12a).—A dry mixture of 14.6 g (0.063 mol) of 2-amino-5-chlorobenzophenone, 5.9 g (0.196 mol) of paraformaldehyde, and 12.4 g (0.191 mol) of KCN was treated with 110 ml of glacial HOAc, and the suspension was stirred for 1 hr. There was a spontaneous temperature rise to 41° at first, and later formation of a thick suspension of yellow solid. The suspension was treated with 1700 ml of water and stirred for 0.8 hr, and the crude material was collected and washed with a number of portions of water. After air drying the crude, voluminous product (18 g, mp *ca.* 168–175°) was triturated with sufficient dry ether to provide a filterable suspension, and collected to give 16.0 g (94%) of yellow crystals: mp 177–180°, raised to 182–183° on further recrystallization from ether; ir 2.99 (moderate to weak) and 6.14 μ; uv 234 nm (ε 32,930), 382 (7070), and inflection at 256; nmr ($CDCl_3$) δ 8.5 (t, 1, slow D_2O exchange, NH), 7.7–6.7 (m, 8, ArH), and 4.2 (d, 2, J = 6.5 Hz, methylene).

Anal. Calcd for $C_{15}H_{11}ClN_2O$: C, 66.54; H, 4.10; N, 10.35. Found: C, 66.52; H, 4.04; N, 10.24, 10.52.

The compound developed a bright red color when treated with 18% hydrochloric acid, but did not readily dissolve. The same product, together with 2-acetylamino-5-chlorobenzophenone (colorless, mp 117–119°), was obtained when 12 g of **11** and 2 g of KCN in 50 ml of acetic anhydride and 100 ml of glacial HOAc were heated for 2 hr on a steam cone; evaporation to *ca.* 75 ml volume gave crystals which were collected, washed with water, and recrystallized from ether as yellow crystals, mp 179–180°, having the same spectra as the first sample of **12**.

The carbinol corresponding to **12a**, 2-(α-hydroxybenzyl)-4-chloroanilinoacetonitrile, was prepared by reduction of **12a** with excess $NaBH_4$ in methanol (heated for 0.5 hr), isolated by treatment with water and extraction with ether, and recrystallized from ether–ligroin as colorless crystals: mp 140–142°; gradual decomposition to a gum on standing; ir 2.93–2.97, 4.43, and 6.20–6.29 μ; uv 249 nm (ε 14,570) and 300 (2810); nmr ($CDCl_3$) δ 7.5–6.6 (m, 8, ArH), 5.82 (s, 1, methine), 5.3 (t, 1, very broad, rapid D_2O exchange, NH), 4.02 (d, 2, J = 6.5 Hz, methylene), and 2.7 (s, 1, D_2O exchange, OH).

Anal. Calcd for $C_{15}H_{13}ClN_2O$: C, 66.05; H, 4.80; N, 10.27. Found: C, 65.70; H, 5.07; N, 10.36.

α-(2-Benzoyl-4-chloroanilino)acetamide (12b).—To a solution prepared by adding 6 g of paraformaldehyde to 11 g of KCN in 80 ml of water was added 21 g of 2-amino-5-chlorobenzophenone and enough ethanol (*ca.* 300 ml) to dissolve the material. The solution was refluxed gently on a steam cone for 0.5 hr, then evaporated on a steam cone for 1 hr to a volume of 200 ml. After dilution with water, the yellow oil was extracted with ether. The ether solution was washed with three portions of water, dried ($MgSO_4$), and evaporated to a smaller volume. The crystals which separated were collected and washed with ether: 1.2 g of bright yellow needles; mp 222–225°, raised to 226–228° on recrystallization from ethyl acetate or ethanol; ir 2.90, 3.04, 3.15, 5.96, and 6.13 μ; uv 233 nm (ε 27,150), inflection at 272, and 395 (6420); nmr (DMSO) δ 8.63 (t, 1, slow D_2O exchange, NH), 7.7–6.6 (m, 10, 2 slow D_2O exchanges, ArH and $CONH_2$), 3.86 (d, 2, J = 5 Hz, methylene).

Anal. Calcd for $C_{15}H_{13}ClN_2O_2$: C, 62.39; H, 4.54; N, 9.70. Found: C, 62.13; H, 4.83; N, 9.70.

The same product, again in low yield (0.6 g), was obtained when 5 g of bisanilinomethane (11) was heated (100°) with aqueous alcoholic KCN solution for 10 hr.

Ester 12c.—Nitrile **12a** was refluxed for 1 hr with 50–100 parts of saturated, methanolic HCl, and the neutral product was isolated as usual, after distillation *in vacuo* of most of the excess reagent, as an oil: ir 5.73 and 6.12–6.14 μ; uv 235 nm (ε 29,880), inflections at 260, 272, and 390 (7100).

Ester 12d was prepared similarly using ethanol, as crystals, mp 103–106° (lit.[3] mp 104–106°).

1,2-Dihydro-4-phenyl-6-chloroquinazoline 3-Oxide (13).[17]—A solution of 1.6 g of $NaHSO_3$ in 20 ml of water was combined with 2.1 ml of 36% formalin, 1.4 g of β-oxime **10c** and 15 ml of DMF were added, and the solution was heated on a steam cone for 0.5 hr and let stand overnight. A solution of KCN (3.8 g in 20 ml of water) was added and heating was resumed for 10 min, resulting in separation of yellow needles which were collected, washed with water, and dried, yield 1.1 g, mp 179–182°. Trituration with a small amount of methanol raised the melting point to 183–187°. A pure sample, recrystallizing from ethyl acetate as cottony, yellow needles, had mp 185–187°; ir 3.13 (moderate), 6.20, and 6.67 μ; uv 234 nm (ε 21,000), 248 (19,000), and 382 (3300) with inflection at 305 (7000); nmr ($CDCl_3$) δ 7.7–6.63 (m, 8, ArH) and 5.04 (s, 2, methylene); NH discerned only on D_2O exchange.

Anal. Calcd for $C_{14}H_{11}ClN_2O$: C, 64.99; H, 4.29; N, 10.83. Found: C, 64.81; H, 4.31; N, 10.81.

The experiment was repeated, omitting the KCN treatment, to give on dilution with water the same compound **13**.

The same compound was isolated, in lower yield, from (a) treatment of **14** with aqueous, methanolic KCN, (b) from reaction of **12a** with a neutral, aqueous, alcoholic solution of hydroxylamine at room temperature, and (c) from mixtures of α- and β-oximes **10b,c** with HCHO under various conditions.

The dihydroquinazoline oxide was $FeCl_3$ negative, and gave with HCl a bright red, unstable, sparingly water-soluble hydrochloride.

A sample of 6-chloro-1,2-dihydro-2,2-dimethylquinazoline 3-oxide,[18] prepared for comparison with **13** by allowing a solution of oxime **10c** in acetone to stand at room temperature for 9 days, consisted of yellow crystals: mp 234–236°; ir 3.09 (moderate) and 6.26 μ (moderate to weak); uv 234 nm (ε 23,140), inflection at 252 (20,610), 294–304 (7390), and 390 (3940); nmr (DMSO) δ 7.7–6.4 (m, 9, 1 D_2O exchange, ArH and NH) and 1.55 (s, 6, CH_3).

7-Chloro-1,2-dihydro-5-phenyl-3,1,4-benzoxadiazepine (14).—A solution of 8 g of oxime **10b** (containing a small amount of **10c**) and 1.2 g of paraformaldehyde in 110 ml of ethanol and 1 ml of HOAc was refluxed on a steam cone for 5.5 hr. Evaporation of the alcohol gave a green-orange syrup which crystallized on standing with dry ether. The crude, yellowish crystals were collected and triturated with methanol, which removed most of the yellow by-product, giving 5.2 g of finely divided crystals, mp 180–182° dec. Recrystallization from acetone afforded a pure sample of **14** as colorless crystals: mp 181–182° dec; ir 2.92 (moderate) and 6.25 μ (weak, sharp); uv 250 nm (ε 22,250), 304 (5220), and 376 nm (1410); nmr (DMSO) δ 7.6–6.7 (m, 8–9, ArH and NH) and *ca.* 5.1 (2, methylene).

Anal. Calcd for $C_{14}H_{11}ClN_2O$: C, 64.99; H, 4.29; N, 10.83. Found: C, 65.05; H, 4.35; N, 10.85.

From the methanol filtrate of the foregoing purification on evaporation there was obtained a small sample of **13**, yellow crystals, mp 175–178°, spectra the same as those of the preceding sample of that compound.

Compound **14** was $FeCl_3$ negative. In the presence of 10–15% hydrochloric acid it gradually became red and eventually was hydrolyzed back to oxime **10b**.

4-Phenyl-6-chloroquinazoline (16).—A sample (0.5 g) of **13** in acetic anhydride (15 ml) was heated for 0.5 hr on a steam cone and the solution was evaporated. The residue crystallized with the aid of ether to give a quantitative yield of **16** as colorless needles: mp 139–140°; ir 6.25 (weak) and 6.43–6.51 μ; uv 229 nm (ε 42,740), 272 (7830), and 326 (6400).

Anal. Calcd for $C_{14}H_9ClN_2$: C, 69.86; H, 3.77; N, 11.64. Found: C, 69.84; H, 3.85; N, 11.53.

Preparation of 16. A. Leuckart Reaction.—A solution of 20 g of **10a** and 30 g of $HCOONH_4$ in 100 ml of $HCONH_2$ and 75 ml of HCOOH (97–100%) was distilled (1 hr) until the vapor temperature reached 175°, then refluxed for 5 hr, cooled, and poured into 300 ml of ice–water. The crystals of the 6-chloro-3,4-dihydro-4-phenylquinazoline formic acid salt (28 g) were collected, washed with water, and dried, mp 139–141° (from EtOAc).

Anal. Calcd for $C_{15}H_{13}ClN_2O_2$: C, 62.39; H, 4.50; N, 9.70. Found: C, 62.18; H, 4.66; N, 9.54.

Treatment of the salt with dilute NaOH solution gave 6-chloro-3,4-dihydro-4-phenylquinazoline (**20**) as crystals from aqueous methanol: mp 176–178° (lit.[20,22] mp 173–174°); ir 3.18 (moderate), 6.23, 6.29, and 6.47 μ; uv 226 nm (ε 17,250) and 294 (8300).

B. Aromatization.—Solution of 11.2 g of **20** from A in 1 l. of cymene containing 5 g of 10% Pd/C catalyst was boiled for 10 min to remove water and refluxed for 1.5 hr. The hot suspension was filtered, the filtrate was evaporated, and the crude product (4.7 g) was recrystallized from methanol to give **16** as very pale yellow needles, mp 138.5–139°, mixture melting point with **16** prepared from **13** undepressed and spectra identical.

Compound **16** can also be prepared from the corresponding 2-chloro derivative.[21]

2-*N*-(Cyanomethyl)amino-5-chlorobenzophenone Oxime (18a).—Formaldehyde bisulfite solution was prepared from 23.4 g (0.225 mol) of $NaHSO_3$ in 45 ml of water and 20 ml (0.26 mol) of 36% formalin, α-oxime **10b** (23.4 g, 0.096 mol) and DMF (115 ml) were added, and the mixture was heated on a steam cone with stirring for 0.8–1 hr to give a somewhat turbid, yellow solution. On standing overnight at room temperature, the solution deposited only a small amount of insoluble material. The anilinomethanesulfonate solution was treated with a solution of 17.5 g (0.27 mol) of KCN in 90 ml of water and warmed gently on a steam cone with swirling for 0.7 hr. The cooled suspension was filtered to remove precipitated, water-soluble salts (34 g), and the rather dark filtrate was diluted with *ca.* 1.5 l. of water. The crude product was extracted with ether; the ether solution was washed with five portions of water, dried ($MgSO_4$), and evaporated without heating the residue above *ca.* 60°. Trituration with ether afforded two crops of crystalline **18a** totaling 10.5 g (39%), mp 174–177°. A sample recrystallized from methanol had mp 179.5–181° (decomposition follows on further heating); the mixture melting point with **10b** (mp 177–179°) was 150–155° (depressed); ir 3.01–3.02 (intense), 4.42 (weak, sharp), and 6.27–6.34 μ (moderate to weak); uv 245 nm (ε 24,940), 292 (2210), and 309 (2480); nmr (DMSO) δ 11.6 (s, 1, D_2O exchange, NOH), 7.6–6.8 (m, 8, ArH), 5.36 (t, 1, D_2O exchange, NH), and 4.22 (d, 2, J = 6.5 Hz, methylene).

Anal. Calcd for $C_{15}H_{12}ClN_3O$: C, 63.05; H, 4.23; N, 14.71. Found: C, 62.94; H, 4.43; N, 14.70.

A difficultly separated mixture of **18a** and **13** was formed when crude oximes **10b,c**, was subjected to the same sequence of reactions.

Ester 18b.—Exposure of samples of **18a** to methanolic HCl under various conditions produced a yellow color and resulted in rapid formation of NH_4Cl. Upon addition of ether and isolation of neutral product by evaporation of the washed ($NaHCO_3$ solution, water) and dried ($MgSO_4$) solution, there were obtained nearly quantitative yields of colorless crystals (from ether): mp 129–132°; ir 2.95, 3.11 (broad), and 5.70 μ; uv 249 nm (ε 24,270) and 316 (2280).

Anal. Calcd for $C_{16}H_{15}ClN_2O_3$: C, 60.28; H, 4.74; N, 8.79. Found: C, 60.57; H, 4.71; N, 8.66.

Ester 18c.—A solution of 2 g of **18a** in saturated ethanolic HCl (55 ml) was allowed to stand overnight. Dilution with ether, isolation of the neutral product as usual (2 g), and recrystallization from ether gave colorless crystals: mp 138.5–140° (lit.[3] mp 132–134°); ir 2.96, 3.13 (broad), and 5.76 μ; uv 249 nm (ε 24,310) and 316 (2400); nmr ($CDCl_3$) δ 9.1 (s, 1, D_2O exchange, =NOH), 7.6–6.5 (m, 8, ArH), 4.67 (t, 1, D_2O exchange, NH), 4.18 (q, 2, J = 7 Hz, ester CH_2), 3.89 (d, 2, J = 6 Hz, *N*-methylene), and 1.22 (t, 3, CH_3).

Anal. Calcd for $C_{17}H_{17}ClN_2O_3$: C, 61.35; H, 5.15; N, 8.42. Found: C, 61.49; H, 5.35; N, 8.30.

Hydrogenation of **18a** in ethanolic NH_3 in the presence of Ni gave amine **18d** as crystals from ether: mp 125–130°; ir 3.01 (strong) and 6.29–6.35 μ; uv 250 nm (ε 24,380), 320 (2290), and inflection 292 (2000); nmr δ *ca.* 11 (=NOH signal, D_2O exchange).

Anal. Calcd for $C_{15}H_{16}ClN_3O$: C, 62.17; H, 5.57; N, 14.50. Found: C, 61.81; H, 5.65; N, 14.00.

Compound **17** (*O*,*N*-diacetyl derivative of **10b**) was obtained when samples of **10b** or **14** were heated at 100° with excess acetic anhydride for 0.5 hr. Evaporation of excess reagent and recrystallization from ether gave colorless crystals: mp 175–176°; ir 3.00, 5.66, and 5.90 μ; uv inflection 242 nm (ε 19,280); nmr ($CDCl_3$) δ 8.3–7.0 (m, 9, ArH and D_2O exchange NH), 2.10 (s, 3, CH_3 of *O*-acetyl), and 1.98 (s, 3, CH_3 of *N*-acetyl).

Anal. Calcd for $C_{17}H_{15}ClN_2O_3$: C, 61.73; H, 4.57; N, 8.47. Found: C, 61.73; H, 4.80; N, 8.36.

Compound 19.—A sample (1 g) of **18a** was similarly heated with Ac_2O (30 ml) on a steam cone for 0.5 hr, the reagent was evaporated, and the readily crystallizing residue was triturated with ether and recrystallized from methanol as colorless crystals:

mp 208–210°; ir 3.00 and 5.69 μ; uv 249 nm (ε 27,980) and inflection at 308 (1900); nmr ($CDCl_3$) δ 7.7–6.7 (m, 8, ArH), 5.14 (t, 1, D_2O exchange, NH), 4.13 (d, 2, J = 6.5 Hz, methylene), and 2.07 (s, 3, acetyl).

Anal. Calcd for $C_{17}H_{14}ClN_3O_2$: C, 62.29; H, 4.30; N, 12.82. Found: C, 62.40; H, 4.42; N, 12.72.

2-(*N*-Acetyl-*N*-methylamino)-5-chlorobenzophenone (21b).—To 6.0 g of 56% NaH in 100 ml of DMF was added 29.3 g of **21a**[14] (prepared by warming **10a** with excess Ac_2O on a steam cone for 2 hr, evaporating, and triturating the residue with ether; mp 115°) with cooling (20°), and the mixture was stirred for 10 min; iodomethane (110 ml) was added while the exothermic reaction was controlled (to 70°) over the course of 10 min. The mixture was warmed on a steam cone for 15 min while excess reagent was evaporated, and the mixture was cooled and poured into water. Extraction with ether, evaporation of the washed (water) and dried ($MgSO_4$) ether solution, and trituration with a small amount of ether gave 24 g of crystals: mp 65–71°, raised to 71–73.5° on recrystallization; ir 6.00 μ; uv 246 nm (ε 14,840).

Anal. Calcd for $C_{16}H_{14}ClNO_2$: C, 66.78; H, 4.90; N, 4.87. Found: C, 67.00; H, 4.85; N, 4.86.

6-Chloro-1-methyl-4-phenyl-2-quinolone (22).[49]—A solution prepared by combining 12 g of **21b** in 60 ml of ethanol and 10.5 g of NaOH in 30 ml of water was refluxed for 4.5 hr. Evaporation of the ethanol and treatment with water gave yellow crystals which were collected, washed with water, dried (yield quantitative), and recrystallized from ethanol as yellow needles: mp 145–147°; ir 6.07 μ; uv 237 nm (ε 50,370), 281 (6330), and 342 nm (ε 5980) with inflections at 212, 328, and 352 nm; nmr ($CDCl_3$) δ 7.7–7.3 (m, 8, ArH), 6.72 (s, 1, methine), and 3.75 (s, 3, CH_3).

Anal. Calcd for $C_{16}H_{12}ClNO$: C, 71.24; H, 4.49; N, 5.19. Found: C, 71.29; H, 4.46; N, 4.88.

2-*N*-Methylamino-5-chlorobenzophenone (23).—A solution of 41.5 g of **21b** in 400 ml each of concentrated HCl and glacial HOAc was refluxed for 3 hr and distilled *in vacuo* to remove most of the excess reagents, the residue was treated with water, and the crystalline product was isolated by ether extraction, washing ($NaHCO_3$, H_2O), drying (K_2CO_3), and evaporating the ether: 36.1 g; mp (from EtOH) 94–95° (lit.[50] mp 94–96°); ir 3.02 and 6.18 μ; uv 235 nm (ε 25,390) and 395 (6900).

Anal. Calcd for $C_{14}H_{12}ClNO$: C, 68.43; H, 4.92; N, 5.70. Found: C, 68.71; H, 4.79; N, 5.86.

2-*N*-(Cyanomethyl)-*N*-methylamino-5-chlorobenzophenone (24).—A dry mixture of 19.2 g of **23**, 7.0 g of paraformaldehyde, and 15.2 g of KCN was treated with 200 ml of glacial HOAc, and the suspension was magnetically stirred for 4.5 hr. Dilution with 1.5 l. of water, extraction with ether, and evaporation of the washed ($NaHCO_3$ solution, water) and dried ether solution gave 23.4 g of yellow oil, which crystallized on standing: 89% product by gpc; crystals from MeOH; mp 78–80°; ir 6.01 μ; uv 249 nm (ε 21,640); nmr ($CDCl_3$) δ 7.9–7.3 (m, 8, ArH), 3.84 (s, 2, methylene), and 2.75 (s, 3, NCH_3).

Anal. Calcd for $C_{16}H_{13}ClN_2O$: C, 67.49; H, 4.60; N, 9.84. Found: C, 67.46; H, 4.90; N, 9.84.

Amide corresponding to **24** was obtained on heating a sample of **24** with PPA for 0.5 hr. After treatment with water, the ether-extracted product crystallized on standing as yellow crystals (from ether): mp 110–112°; ir 2.94, 3.13, 5.89, and 6.10 μ; uv 251 nm (ε 23,030) and inflection at 380 (1390); nmr ($CDCl_3$) δ 8.1–7.1 (m, 9, 1 slowly D_2O exchanges NH of $CONH_2$), 5.94 (s, very broad, 1, slowly D_2O exchanges NH of $CONH_2$), 3.78 (s, 2, methylene), and 2.72 (s, 3, NCH_3).

Anal. Calcd for $C_{16}H_{15}ClN_2O_2$: C, 63.47; H, 4.99; N, 9.25. Found: C, 63.73; H, 5.02; N, 9.11.

7-Chloro-2,3-dihydro-1-methyl-5-phenyl-1*H*-1,4-benzodiazepine (25).—A solution of 12 g of **24** in 200 ml of NH_3-saturated ethanol containing *ca.* 20 g of washed Ni catalyst (Grace 28) was shaken under 50 lb of H_2 for 6.5 hr. The filtered solution was evaporated. A solution of the crude residue in dilute HCl was filtered, washed with ether, and made basic by adding NaOH solution, and the base was isolated by extraction with ether and evaporation of the water-washed and dried (K_2CO_3) ether solution to give 8.5 g (75%) of orange oil, crystallizing on standing. Recrystallization from ether or aqueous ethanol afforded slightly orange or colorless crystals: mp 101–103° (lit.[31,32] mp 95–97°, 97–99°); ir 5.93 (weak), 6.20 μ; uv 229 nm (ε 21,810) and 358 (1870) with inflection at 248 (19190); nmr ($CDCl_3$) δ 7.75–6.8 (m, 8, ArH), 3.67 (m, 4, CH_2CH_2), and 2.77 (s, 3, NCH_3).

Anal. Calcd for $C_{16}H_{15}ClN_2$: C, 70.97; H, 5.58; N, 10.35. Found: C, 71.09; H, 5.52; N, 10.13.

The corresponding hydrochloride was precipitated from ether with ethanolic HCl and recrystallized from ethanol–ether as yellow crystals: mp 257–258° dec; ir 3.79, 5.52, and 6.12 μ; uv 250 nm (ε 21,410) and 455 (4950).

Anal. Calcd for $C_{16}H_{15}ClN_2 \cdot HCl$: C, 62.55; H, 5.25; N, 9.12. Found: C, 62.83; H, 5.36; N, 9.06.

The sparingly water-soluble hydrochloride of *N*-(2-aminoethyl)-*N*-methyl-2-benzoyl-4-chloroaniline was obtained from **25** with hydrochloric acid as colorless crystals from water: mp 258–261° dec; ir 2.92, 6.23 μ; uv 236 nm (ε 37,520) and 262 (9890) with inflections at 230 (36,920) and 300 (7160).

Anal. Calcd for $C_{16}H_{17}ClN_2O \cdot HCl$: C, 59.08; H, 5.58; N, 8.62. Found: C, 59.74; H, 5.32; N, 8.81.

5-Chloro-1-methyl-3-phenylindole-3-carbonitrile (26a).—Nitrile **24** (5.1 g) was added to a solution of Na (0.45 g) in methanol (50 ml) and the solution was refluxed for 0.2 hr. The suspension of crystals was cooled and the product was collected and washed with methanol: yield 4.4 g (92%) of colorless crystals; mp 132–133°, raised to 134–135° (lit.[34] mp 131°) on recrystallization from methanol; ir 4.50 (moderate to intense, sharp) and 6.24 μ (weak, sharp); uv 238 nm (ε 42,000), 301 (13,500), and 327 (8800); nmr ($CDCl_3$) δ 7.9–7.3 (m, 8, ArH) and 3.92 (s, 3, NCH_3).

Anal. Calcd for $C_{16}H_{11}ClN_2$: C, 72.04; H, 4.16; N, 10.51. Found: C, 72.17; H, 4.36; N, 10.52.

The same indole **26a** was obtained when **24** was allowed to stand with (a) dry HCl in ether or (b) a solution of $MeNH_2$ in MeOH. Compound **26a** resisted reaction with (a) refluxing methanolic HCl, (b) PPA at 100°, and (c) refluxing, concentrated HCl–glacial acetic acid.

Amidoxime 26b.—A solution of hydroxylamine was prepared from 2.73 g of Na in 300 ml of ethanol and 8.2 g of $H_2NOH \cdot HCl$, nitrile **26a** (4.2 g) was added, and the whole was refluxed for 6 hr. The filtered solution was evaporated, and a twice filtered and concentrated, dry ether solution of the material was gassed gently with dry HCl to give 3.5 g (66%) of the hydrochloride as cream-colored crystals: mp 191–193° dec, raised to 195–197° on recrystallization from ethanol–ether; ir 2.95, 3.05–3.18 (bonded), 5.99–6.03 (doublet), and 6.23 μ; uv 227 nm (ε 35,680) and 298 (9660) with inflections at 212 (29,760) and 232 (35,110).

Anal. Calcd for $C_{16}H_{14}ClN_3O \cdot HCl$: C, 57.15; H, 4.50; N, 12.50. Found: C, 57.27; H, 4.59; N, 12.51.

Compound **26b** was also prepared directly from **24** (2.9 g) by similar reaction (4 hr reflux) with ethanolic hydroxylamine (from 3.5 g of $H_2NOH \cdot HCl$ and 1.15 g of Na), and isolated as the hydrochloride (1.5 g), mp 192–193° (from ethanol–ether), spectra identical with those of the above sample.

Amide 26d.—The preceding experiment was repeated with 3 g of **26a**, and, after concentration of the filtered ethanol solution, water was added to the crude, residual base, resulting in partial hydrolysis. Together with 2.1 g of ether-soluble, crude amidoxime **26b** ($FeCl_3$, green test) there was isolated 1.1 g of ether-insoluble, colorless crystals of **26d** ($FeCl_3$, test negative): mp 185–190°, raised to 193–194° on recrystallization from ethanol (lit.[34] mp 192°); ir 2.92, 3.04, 3.16, and 6.04 μ.

Amine 26c.—Hydrogenation of either **26a** or **26b** in ethanol with Ni catalyst was carried out as described in preparation of **25**. The crude amine was converted to the corresponding hydrochloride, recrystallizing from ethanol–ether as colorless crystals: mp 260–262° dec (lit.[34] mp 256° dec); ir broad NH bands; uv 236 nm (ε 36,000) and 263 (9800) with inflections at 235 (36,000), 284 (8500), and 300 (7100); nmr (DMSO) δ 8.92 (broad s, 3, D_2O exchange, $NH_2 \cdot HCl$), 7.8–7.2 (m, 8, ArH), 4.25 (s, 2, methylene), and 3.94 (s, 3, NCH_3).

Anal. Calcd for $C_{16}H_{15}ClN_2 \cdot HCl$: C, 62.55; H, 5.25; N, 9.12. Found: C, 62.39; H, 5.45; N, 8.82.

5-Methyl-6,11-morphanthridinedione (28b).—A mixture of 33 g of **28a**[35,37] and 150 ml of DMSO was treated with 17 g of potassium *tert*-butoxide and stirred for 10 min; to the resulting solution was added 60 ml of CH_3I, and the reaction was allowed to proceed exothermically. The intense green-brown color was discharged. After 15 min the solution was warmed briefly to *ca.* 80° and allowed to stand for 1 hr while cooling gradually to room temperature. Water (1 l.) was added, the oil was extracted with ether,

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(50) L. H. Sternbach, R. I. Fryer, W. Metlesics, G. Sach, and A. Stempel, *J. Org. Chem.*, **27**, 3781 (1962).

and the ether solution was washed with two portions of water, dried ($MgSO_4$), and evaporated, yield 26 g (74%) of crude crystals, mp 80–84°, suitable for further work. A pure sample, recrystallized from ether or methanol, had mp 98–99°; ir 6.01, 6.14, and 6.25 μ; uv 228 nm (ε 27,800) and inflections at 244 (20,580), 272 (7550), and 324 (1520).

Anal. Calcd for $C_{15}H_{11}NO_2$: C, 75.93; H, 4.67; N, 5.90. Found: C, 76.25; H, 4.83; N, 6.01.

2-Chloro-5-methyl-6,11-morphanthridinedione (28c) was obtained by similar methylation of 2-chloro-6,11-morphanthridinedione[35] in 79% yield as colorless crystals from ethanol: mp 154–155° (lit.[11,35] mp 148–151°); ir 5.98 and 6.10 μ; uv 225 nm (ε 26,000) and 331 (1200) with inflections at 240–245 (20,000) and 280–290 (1800).

Anal. Calcd for $C_{15}H_{10}ClNO_2$: C, 66.31; H, 3.79; N, 5.13. Found: C, 66.30; H, 3.71; N, 5.16.

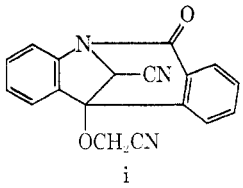
Compound 28d was obtained by similar alkylation of **28a** with benzyl chloride in 78% yield as colorless crystals from ethanol: mp 106–107°; ir 5.95, 6.08, and 6.27 μ; uv inflections at 224 nm (ε 27,960), 274 (7230), and 318 (1720).

Anal. Calcd for $C_{21}H_{15}NO_2$: C, 80.49; H, 4.83; N, 4.47. Found: C, 80.20; H, 4.94; N, 4.20.

Compound 28e.—Morphanthridinedione **28a** (18.8 g) in 90 ml of DMSO was treated with potassium *tert*-butoxide (10.0 g), the suspension was swirled until the materials dissolved, and 7 ml of chloroacetonitrile was added. A strongly exothermic reaction ensued and the intense green color was discharged. After *ca.* 15 min, the solution was reheated to 80° briefly and allowed to stand for 1 hr and cool slowly to room temperature. After addition of water (1 l.) the crude, neutral product was isolated by extraction with ether as for **28b**. The concentrated ether solution was filtered to remove insoluble material and evaporated. The slowly crystallizing residue on trituration with methanol gave 7.2 g (33%) of crystals, mp *ca.* 150°. Recrystallization from methanol afforded material: mp 171–173° after drying *in vacuo;* ir 6.02, 6.11, and 6.28 μ and a barely visible CN signal at *ca.* 4.47 μ; uv 221 nm (ε 30,000) and 274 (6320); nmr ($CDCl_3$) δ 7.8–7.2 (m, 8, ArH) and 4.8 (s, 2, methylene).

Anal. Calcd for $C_{16}H_{10}N_2O_2$: C, 73.27; H, 3.84; N, 10.68. Found: C, 73.45; H, 3.92; N, 10.63.

When this reaction was conducted in essentially the same way, using 15.6 g of **28a**, 8 g of potassium *tert*-butoxide, and 14 ml of $ClCH_2CN$, the isolated, crude material contained 2.9 g of recovered **28a** (mp 250°), 6.5 g of **28e**, and 0.5 g of material, mp *ca.* 215–216°, which was sparingly soluble in alcohols. A pure sample of the latter material (recrystallized from ethanol) had mp 225–226°. Analysis and spectra indicated that its structure was i: ir 4.46 (very weak), 6.09, and 6.26 μ; uv 269–274 nm



i

(ε 3180) with strong end absorption; nmr (DMSO) δ 8.1–7.3 (m, 8, ArH), 5.15 (q, 2, J_{AB} = 17 Hz, methylene), and 4.72 (s, 1, methine).

Anal. Calcd for $C_{18}H_{11}N_3O_2$: C, 71.75; H, 3.68; N, 13.95. Found: C, 71.55; H, 4.10; N, 13.78.

The structure of this compound was confirmed by independent synthesis of an identical sample, mp 227–229° (low yield), by treatment of **28e** with $ClCH_2CN$ and potassium *tert*-butoxide in THF (15-min reflux). In this reaction there was also formed regenerated **28a**, mp 249–251°, identical with authentic sample.

Methyl *o*-2-Aminobenzoylbenzoate (29a, R′ = CH_3). A. Hydrolysis.—Hydrolysis of 68 g of **28a** in 100 ml of methanol with 300 ml of 10% aqueous NaOH by warming for 0.8 hr on a steam cone gave a solution which was diluted with 400 ml of water, chilled, and slowly acidified with 18% HCl. The crystals were collected, washed with water, and air dried, to give 73.8 g of bright yellow *o*-2-aminobenzoylbenzoic acid, mp 190–200° (effervescing and resolidifying to give **28a**), as described in the literature.[40]

B. Esterification.—A solution of 73.5 g of acid from A in 3 l. of dry methanol was saturated with dry HCl and allowed to stand for 6 days. Most of the methanol was removed by distillation *in vacuo* on a stream cone. To the cooled residue ether was added, then water and $NaHCO_3$ solution to neutralize, and the ether extract, after washing with water and drying ($MgSO_4$), was evaporated to yield 56.5 g (73%) of yellow crystals: mp 113–117°, raised to 115–117° on recrystallization from ether; ir 2.92, 3.02, 5.84, and 6.10 μ; uv 227 nm (ε 26,900) and 372 (6400) with inflections at 256 (9120) and 280 (1990); nmr ($CDCl_3$) δ 8.2–6.1 (m, 10, 2 D_2O exchange, ArH and NH_2) and 3.68 (s, 3, CH_3).

Anal. Calcd for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.13; N, 5.49. Found: C, 70.57; H, 5.11; N, 5.49.

Acid 29b (R′ = H) was prepared from **28b** by procedure A of the preceding experiment in quantitative yield as yellow crystals from methanol: mp 207–208° dec; ir 3.00 (moderate), 3.84–4.31 (moderate to weak), 5.82, and 6.19 μ; uv 210 nm (ε 27,340), 226 (27,000), 261 (8300), and 390 (7600); nmr (DMSO) δ 13–12 (broad s, 1, D_2O exchange, COOH), 9.0–6.3 (m, 9, 1 D_2O exchange, ArH and NH), and 2.9 (s, 3, NCH_3).

Anal. Calcd for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.13; N, 5.49. Found: C, 70.70; H, 5.36; N, 5.52.

The *N*-chloroacetyl derivative of **29b** (R′ = H), from **29b** (R′ = H) with chloroacetyl chloride, after recrystallization from ether had mp 173–175°; ir 5.83, 6.00 and 6.13 μ; uv inflection at 285 nm (ε 3380).

Anal. Calcd for $C_{17}H_{14}ClNO_4$: C, 61.54; H, 4.25; N, 4.22. Found: C, 61.65; H, 4.25; N, 4.43.

Acid 29c (R′ = H).—Similar ring opening of 46 g of **28c** in 500 ml of methanol with 250 ml of 10% NaOH solution (2 hr heating on steam cone) and careful HCl acidification of the cooled, diluted solution gave 48 g (97%) of yellow crystals: mp 215–218° dec, raised to 221–223° dec on recrystallization from ethanol; ir 2.98, 3.85, 5.80, and 6.19 (6.27) μ; uv 228 nm (ε 30,550), 263 (8610), and 400 (7420); nmr (DMSO) δ 13–12 (broad s, 1, D_2O exchange, COOH), 8.8–6.7 (m, 8, 1 D_2O exchange, ArH and NH), and 2.94 (d, 3, NCH_3).

Anal. Calcd for $C_{15}H_{12}ClNO_3$: C, 62.18; H, 4.18; N, 4.84. Found: C, 61.87; H, 4.46; N, 4.79.

Acid 29d (R′ = H) was obtained from similar hydrolytic ring opening of **28d** as yellow crystals from ether: mp 162–164° dec; ir 3.01 (moderate), 3.78–3.95 (weak), 5.92, and 6.14 μ; uv 229 nm (ε 28,430), 261 (9540), and 386 (8000).

Anal. Calcd for $C_{21}H_{17}NO_3$: C, 76.12; H, 5.17; N, 4.23. Found: C, 76.00; H, 5.32; N, 4.10.

Acid 29e (R′ = H).—Potassium *tert*-butoxide powder (1 g) was exposed to atmospheric moisture for 1 hr and added to a solution of 2 g of **28e** in 50 ml of THF. The deep reddish-brown mixture was heated on a steam cone for 15 min. The THF was evaporated, the residue was taken up in water and acidified with dilute HCl, and the yellow-brown precipitate was extracted with ether. The washed and dried ether solution, after being evaporated to small volume, gave several small crops of brownish-yellow crystals, mp *ca.* 190–197° dec. Further recrystallization from ether afforded yellow crystals: mp 203–205° dec; ir 2.98, 5.92, and 6.12 μ; uv 225 nm (ε 26,430), 257 (8700), and 365 (6430) with inflection at 282; nmr (DMSO) δ 13–12 (broad, 1, D_2O exchange, COOH), 8.8 (t, 1, J = 6.5 Hz, D_2O exchange, NH), 8.1–6.4 (m, 8, ArH), and 4.6 (d, 2, J = 6.5 Hz, collapse to s on D_2O exchange of NH, methylene).

Anal. Calcd for $C_{16}H_{12}N_2O_3$: C, 68.56; H, 4.32; N, 10.00. Found: C, 68.62; H, 4.64; N, 9.69.

Ester 29e (R′ = CH_3).—After 1.5 g of **28e** was treated with 0.7 g of potassium *tert*-butoxide in 100 ml of THF and warming for 10 min, iodomethane (10 ml) was added and the solution was refluxed for 1 hr. The evaporated (*in vacuo*) suspension was treated with water, and the product was extracted with ether and isolated as usual to give 0.75 g of pale yellow crystals (mp *ca.* 130°), purified by recrystallization from methanol: mp 142–143°; ir 3.01, 5.80, and 6.10 μ with barely discernible CN peak at *ca.* 4.46 μ; uv 226 nm (ε 26,030), 257 (8980), and 367 (6550), with inflections at 282 (1910); nmr ($CDCl_3$) δ 8.98 (t, 1, J = 6.6 Hz, D_2O exchange, NH), 8.2–6.5 (m, 8, ArH), 4.26 (d, 2, J = 6.6 Hz, collapse to s on D_2O exchange of NH, methylene), and 3.67 (s, 3, CH_3).

Anal. Calcd for $C_{17}H_{14}N_2O_3$: C, 69.37; H, 4.80; N, 9.52. Found: C, 69.53; H, 4.79; N, 9.54.

Ester 29b (R′ = CH_3) was prepared by esterification of **29b** (R′ = H) (18 g) with 2 l. of methanolic HCl (let stand 5 days) following procedure B as for **29a** (R′ = CH_3): yield 17.3 g of yellow crystals from methanol; mp 87–89°; ir 3.01, 5.80, and 6.15 μ; uv 224 nm (ε 29,950), 251–263 (8180), and 391 (8290)

nmr ($CDCl_3$) δ 8.75 (s, 1, broad, D_2O exchange, NH), 8.2–6.3 (m, 8, ArH), 3.7 (s, 3, ester CH_3), and 2.98 (s, 3, NCH_3).

Anal. Calcd for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.18; H, 5.58; N, 4.96.

Ester 29c (R′ = CH_3) was prepared from **29c** (R′ = H) by the same procedure, in 95% yield as yellow crystals (from MeOH or EtOH): mp 107–108°; ir 2.99, 5.79, and 6.08–6.15 μ (doublet); uv 230 nm (ε 31,860), 262 (8700), and 403 (7340); nmr ($CDCl_3$) δ 8.7 (t, 1, J = 4.5 Hz, D_2O exchange, NH), 8.2–6.6 (m, 7, ArH), 3.7 (s, 3, ester CH_3), and 2.93 (d, 3, J = 4.5 Hz, collapses to s on D_2O exchange of NH, NCH_3).

Anal. Calcd for $C_{16}H_{14}ClNO_3$: C, 63.26; H, 4.65; N, 4.61. Found: C, 63.40; H, 4.77; N, 4.53.

Phthalimidinospiro[3,4′]-1-methyl-2-oxo-6-chloro-1,2,3,4-tetrahydroquinazoline (30c).—Fusion of 5 g of **29c** and 6 g of urea at 210° for 1.2 hr gave, on trituration of the cooled melt with ether or ethanol, 3.1 g of crystals, mp *ca.* 330° dec. A sample recrystallized from aqueous DMF had mp 338–340° dec; ir bonded NH (3.18, 3.27), 5.83, and 5.97 μ; uv 250 nm (ε 17,400) and 296 (2130) with inflection at 211 (41,920).

Anal. Calcd for $C_{16}H_{12}ClN_3O_2$: C, 61.25; H, 3.86; N, 13.39. Found: C, 61.13; H, 3.95; N, 13.40.

Compound 30a, similarly prepared from **29a** (R′ = CH_3) and recrystallized from ethanol, had mp 304–305° (lit.[42] mp 305°); ir bonded NH (3.14), 3.28, and 5.90–5.98 μ (doublet); uv 241 nm (ε 14450) and 284 (2250) with inflection at 289 (1990).

Phthalido-3-spiro[3,4′]-1-methyl-1,2-dihydro-3,1-benzoxazine (31).—A suspension of acid **29b** (R′ = H) (2.7 g) and paraformaldehyde (1.2 g) in 20 ml of glacial HOAc was warmed on a steam cone for 10 min. The resulting solution was allowed to stand for 3 hr and cool. Addition of 100 ml of water gave a nearly colorless oil which solidified and was collected, washed with water, and dried: 3.1 g of crystals; mp 150–152.5°, raised on recrystallization from ether or ethanol to 152–154°; ir 5.66 μ; uv 283 nm (ε 2290) and 301 (2510) with a series of inflections at 212, 230, and 244; nmr ($CDCl_3$) δ 8.1–6.6 (m, 8, ArH), 4.93 (q, 2, J_{AB} = 9 Hz, methylene), and 3.1 (s, 3, NCH_3).

Anal. Calcd for $C_{16}H_{13}NO_3$: C, 71.90; H, 4.90; N, 5.24 Found: C, 71.99; H, 5.14; N, 5.01.

The same compound was obtained when KCN was also added to the reaction.

***N*-Bromoacetylamino(keto ester) 32a (R′ = CH_3).**—Compound **29a** (R′ = CH_3) (2 g) in 300 ml of dry ether and 1 ml of Et_3N was treated with 2 ml of $BrCH_2COBr$ with swirling, and the suspension was allowed to stand for 1 hr. After washing with water, drying ($MgSO_4$), and evaporating the ether, there was obtained 2.1 g of crystals: mp 144–146°; ir 3.20 (weak), 5.83, 5.97, and 6.04 μ; uv 233 nm (ε 27,450), 264 (12,360), and 325 (5420); nmr ($CDCl_3$) δ 11.5 (s, 1, D_2O exchange, NH), 8.6–7.0 (m, 8, ArH), 4.31 (s, 2, methylene), and 3.60 (s, 3, ester CH_3).

Anal. Calcd for $C_{17}H_{14}BrNO_4$: C, 54.27; H, 3.75; N, 3.72. Found: C, 54.29; H, 3.79; N, 3.74.

***N*-Bromoacetylamino(keto acid) 32b (R′ = H).**—A solution of 4.8 g of **29b** (R′ = H) in 30 ml of THF was treated with 2 ml of $BrCH_2COBr$ and the suspension was let stand for 1 hr. Filtration gave **29b** (R′ = H) hydrobromide as colorless crystals from ethanol: mp 212–214° dec; ir 3.70, 4.19, 5.91 and 6.02–6.07 μ (doublet); uv 226 nm (ε 26,430), 261 (7950), and 390 (7250).

Anal. Calcd for $C_{15}H_{14}BrNO_3$: C, 53.59; H, 4.20; N, 4.17. Found: C, 53.83; H, 4.06; N, 3.90.

The filtrate was diluted with ether, filtered clear, and evaporated and the residue was recrystallized from ethyl acetate–ether as rather unstable, pale yellow crystals of **32b** (R′ = H), mp 143–145°, ir 5.85, 6.01, 6.16, and 6.28 μ.

Anal. Calcd for $C_{17}H_{14}BrNO_4$: C, 54.27; H, 3.75; N, 3.72. Found: C, 54.26; H, 4.07; N, 3.67.

***N*-Bromoacetylamino-*N*-methyl(keto ester) 32b (R′ = CH_3).**—Similar acylation of 10.7 g of **29b** (R′ = CH_3) in 300 ml of dry ether and 5 ml of Et_3N with 9.8 ml of $BrCH_2COBr$ gave 12.7 g of crude, pale yellow, glassy material after evaporation of the water-washed and dried ether solution, crystallizing in the presence of ether to give colorless crystals: mp 96–97.5°; ir 5.83 and 5.97–6.01 μ (doublet); uv inflections at 230 nm (ε 16,360), 274 (2950), and 284 (2780); nmr ($CDCl_3$) δ 8.1–7.2 (m, 8, ArH), 3.72 (s, 5, methylene and ester CH_3), and 3.2 (s, 3, NCH_3).

Anal. Calcd for $C_{18}H_{16}BrNO_4$: C, 55.40; H, 4.13; N, 3.59. Found: C, 55.21; H, 4.30; N, 3.68.

Bromoacetylation of **29c** (R′ = H and CH_3) was conducted similarly; the crude *N*-bromoacetyl derivatives **32c** were usually not purified but converted directly to **34b** and **35b**, respectively.

Crude **32c** (R′ = CH_3) had ir 5.79 and 5.96–5.99 μ; uv 211 nm (ε 32,800), 397 (870), and inflections at 233 (21,810) and 284 (3350).

Methyl *o*-(2-*N*-Cyanomethyl-*N*-methylamino)benzoylbenzoate (33b).—To 30.4 g of ester **29c**, 9 g of paraformaldehyde, and 19.5 g of KCN was added 250 ml of glacial HOAc. The mixture was stirred for 5 hr and warmed gently to an average temperature of *ca.* 45–50° during this period. After addition of water to the cooled solution, the oil was extracted with ether, washed thrice with water, and dried (Na_2SO_4). Evaporation gave 38 g of turbid, pale yellow oil which crystallized slowly on standing. Trituration with methanol and recrystallization from ethanol gave pale yellow crystals: mp 75.5–78°; ir 5.87 and 6.04 μ; uv 238 nm (ε 19,950) and 368 (1680); nmr ($CDCl_3$) δ 8.0–7.0 (m, 7, ArH), 4.01 (s, 2, methylene), 3.73 (s, 3, ester CH_3), and 2.82 (s, 3, NCH_3).

Anal. Calcd for $C_{18}H_{15}ClN_2O_3$: C, 63.07; H, 4.41; N, 8.17. Found: C, 63.26; H, 4.46; N, 8.08.

Compound 33a.—Similarly conducted Strecker reaction of **29b** (30 g) with intermittent warming on a steam cone for 5 hr gave 35.5 g of viscous, yellow oil which did not crystallize: ir 5.79 and 6.00 μ (no NH band); uv 235 nm (ε 18,220) and 362 (1770).

Phthalido-3-spiro[3,5′]-1-methyl-2-oxo-2,3-dihydro-4,1-benzoxazepine (34a).—Crude **32b** (R′ = H), from bromoacetylation of 2 g of **29b** (R′ = H), was treated with 125 ml of saturated ethanolic NH_3. The deep red solution was allowed to stand for 1 hr, then evaporated on a steam cone, and the residue was treated with dilute NH_4OH. An ether extract of the resulting oil was washed with water, dried ($MgSO_4$), and evaporated, giving 0.9 g of crystals, from ether: mp 176–178°; ir 5.73 and 5.98 μ; uv inflection at 276 nm (ε 3160); nmr ($CDCl_3$) δ 7.9–6.8 (m, 8, ArH), 4.45 (q, 2, J_{AB} = 12 Hz, methylene), and 3.46 (s, 3, NCH_3).

Anal. Calcd for $C_{17}H_{13}NO_4$: C, 69.14; H, 4.44; N, 4.74. Found: C, 69.13; H, 4.47; N, 4.54.

Compound 34b was prepared similarly. Bromoacetylation of 5.8 g of **29c** (R′ = H) in 50 ml of THF and 3 ml of Et_3N with 2.5 ml of $BrCH_2COBr$, filtration, and evaporation of the solution gave crude **32c** (R′ = H). Crude **32c** was treated with a solution of 5 ml of Et_3N in 100 ml of ethanol. The solution, after standing overnight, was evaporated, the residue was triturated with dilute NH_4OH, and the product was collected, washed with water, and recrystallized from ethanol to give 4.4 g of colorless crystals: mp 183–185°; ir 5.76 and 5.96 μ; uv 282 nm (ε 2510) with inflection at 212 (40,650); nmr ($CDCl_3$) δ 8.0–6.8 (m, 7, ArH), 4.46 (q, 2, J_{AB} = 12 Hz, methylene), and 3.43 (s, 3, NCH_3).

Anal. Calcd for $C_{17}H_{12}ClNO_4$: C, 61.92; H, 3.67; N, 4.25. Found: C, 62.08; H, 3.75; N, 4.22.

5-Methyl-6,7-dihydro-13b-hydroxyisoindolo[2,1-*d*][1,4]benzodiazepine-6,9-dione (35a).—Crude **32b** (R′ = CH_3) from bromoacetylation of 10 g of **29b** (R′ = CH_3) was treated with 300 ml of saturated, methanolic NH_3. The solution was allowed to stand overnight at room temperature and evaporated on a steam cone to a volume of *ca.* 80 ml, and the crystals which separated from the concentrated red solution were collected, washed with methanol and water, and air dried, giving 4.4 g (40%) of colorless crystals: mp 234–236° dec (with vigorous gas evolution, deep purple melt), raised to 237–239° dec on careful recrystallization from methanol; ir 2.97 (moderate), 5.85, and 6.08 μ; uv 230 nm (ε 17,130) and 246 (14,290), with inflection at 214 (31,410); nmr (DMSO) δ 7.9–6.8 (m, 9, 1 D_2O exchange, ArH and OH), 3.88 (q, 2, J_{AB} = 13 Hz, methylene), and 3.32 (s, 3, NCH_3).

Anal. Calcd for $C_{17}H_{14}N_2O_3$: C, 69.37; H, 4.80; N, 9.52. Found: C, 69.35; H, 4.85; N, 9.63.

Compound 35b.—Crude bromoacetyl product **32c** (R′ = CH_3), from 11.0 g of **29c** (R′ = CH_3) with 7 ml of $BrCH_2COBr$ in 500 ml of ether and 11 ml of Et_3N, was treated similarly with 350 ml of methanolic NH_3 to give 5.9 g (50%) of colorless crystals (from methanol): mp 239–241° dec; ir 3.07 (moderate), 5.87, and 5.96 μ; uv 250 nm (ε 17,540) with inflection at 230 (15,920); nmr (DMSO) δ 7.9–6.8 (m, 8, 1 D_2O exchange, ArH and OH), 3.96 (q, 2, J_{AB} = 13 Hz, methylene), and 3.36 (s, 3, NCH_3).

Anal. Calcd for $C_{17}H_{13}ClN_2O_3$: C, 62.10; H, 3.98; N, 8.52. Found: C, 62.30; H, 4.09; N, 8.51.

6,7-Dihydro-13b-hydroxyisoindolo[2,1-*d*][1,4]benzodiazepine-6,9-dione.—Compound **32a** (R′ = H) (15.9 g) was treated with

1.3 l. of saturated, methanolic NH_3. The suspension was stirred for 20 hr, and the resulting solution was evaporated to a volume of *ca.* 50 ml. The crystals which separated were collected, washed with ethanol and several portions of water, and dried, yield 1.2 g of colorless crystals, mp 227–229° dec. The compound was recrystallized with difficulty from methanol: mp 253–255° dec; ir 3.04, 3.10, 3.20, and 5.87–5.90 μ with shoulders at 5.83 and 5.99 μ; uv inflections at 216 nm (ϵ 33,610) and 282 (2890).

Anal. Calcd for $C_{16}H_{12}N_2O_3$: C, 68.56; H, 4.32; N, 10.00. Found: C, 68.58; H, 4.62; N, 9.84.

Hydrogenolysis of this compound in glacial HOAc in the presence of 10% Pd/C at 60° gave **6,7-dihydroisoindolo[2,1-*d*][1,4]benzodiazepine-6,9-dione** as colorless crystals from ethanol: mp 269–273° dec; ir 3.12–3.20, 5.83, and 5.96 μ; uv 222 nm (ϵ 20,500) and 230 (20,980) with inflections at 236 (18,390) and 278 (2720); nmr (DMSO) δ 10.3 (s, 1, D_2O exchange, NH), 7,9–7.0 (m, 8, ArH), 6.04 (s, 1, methine), and 4.17 (q, 2, J_{AB} = 15 Hz, methylene).

Anal. Calcd for $C_{16}H_{12}N_2O_2$: C, 72.71; H, 4.58; N, 10.60. Found: C, 72.87; H, 4.96; N, 10.50.

5-Methyl-6,7-dihydro-13b-hydroxyisoindolo[2,1-*d*][1,4]-benzodiazepin-9(13b*H*)-one (35c).—A solution of 8.3 g of **33a** in 200 ml of NH_3-saturated ethanol was hydrogenated (45 lb) at room temperature in the presence of washed Ni catalyst for 8 hr, uptake of *ca.* 1.5 molar equiv of H_2 being observed. After evaporation of the filtered solution, trituration of the residue with ether gave 6.5 g of impure solid which crystallized in the presence of methanol or ethanol and afforded 1.3 g (17%) of pale yellow crystals, mp 175–177°. Alternatively, the crude residue from evaporation was treated with water and the product was extracted with ether. A pure sample (from ethanol) had mp 179–180°; ir 3.00 and 5.94 μ; uv 215 nm (ϵ 24,780) and 250 (8710); nmr ($CDCl_3$) δ 7.9–6.8 (m, 9, 1 D_2O exchange, ArH and OH), 4.2–3.1 (m, 4, CH_2CH_2), and 2.91 (s, 3, NCH_3).

Anal. Calcd for $C_{17}H_{16}N_2O_2$: C, 72.47; H, 5.92; N, 9.68. Found: C, 72.84; H, 5.75; N, 9.99.

The compound dissolved in 15% HCl giving a deep blue solution (λ_{max} 580, and 752 nm) which on standing for several hours became greenish yellow (λ_{max} 435, 590, and 775 nm).

Compound 35d.—Similar Ni-catalyzed hydrogenation of 11.3 g of **33b** in ethanolic NH_3 (7 hr) gave *ca.* 1 g (10%) of colorless crystals (from ethanol): mp 187–189° dec; ir 3.09 and 5.91 μ; uv 215 nm (ϵ 32,100), 255 (6750), 259 (10,710), and inflection at 301 (2010); nmr ($CDCl_3$) δ 7.9–6.9 (m, 8, 1 D_2O exchange, ArH and OH), 4.1–3.0 (m, 4, CH_2CH_2), and 2.85 (s, 3, NCH_3).

Anal. Calcd for $C_{17}H_{15}ClN_2O_2$: C, 64.47; H, 5.24; N, 8.61. Found: C, 64.86; H, 4.90; N, 8.90.

Solutions of this hydroxylactam in strong acids were deep blue, becoming green on standing.

Hydrogenolysis of 35c.—To the deep blue solution of 1.5 g of **35c** in 220 ml of glacial HOAc was added 0.5 g of 10% Pd/C, and the suspension was shaken under H_2 (45 lb) at 50–55° for 1.5 hr. The filtered, nearly colorless solution was evaporated. An ether solution of the residue was washed with $NaHCO_3$ solution and water, dried ($MgSO_4$), and evaporated to give 0.9 g of colorless crystals, mp 141–144°; a pure sample, obtained by recrystallization from methanol, had mp 144–145.5°, undepressed on admixture with **4a** prepared from **3a**; ir, uv, and nmr spectra of the independently prepared **4a** samples were identical.

Similar hydrogenolysis of **35a** in glacial HOAc with 10% Pd/C at 65° for 2 hr gave **5-methyl-6,7-dihydroisoindolo[2,1-*d*][1,4]-benzodiazepine-6,9(13b*H*)-dione** as colorless crystals from methanol: mp 228–230°; ir 5.90 and 6.00 μ; uv 230 nm (ϵ 18,900) with inflections at 222 (18,470), 237 (17,070) and 278 (2270); nmr (DMSO) δ 7.9–6.8 (m, 8, ArH), 5.99 (s, 1, methine), 3.96 (q, 2, J_{AB} = 14 Hz, methylene), and 3.43 (s, 3, NCH_3).

Anal. Calcd for $C_{17}H_{14}N_2O_2$: C, 73.36; H, 5.07; N, 10.07. Found: C, 73.54; H, 5.25; N, 9.87.

1-Methyl-2,3-dihydro-5-(2′-carbomethoxyphenyl)-1,4-benzodiazepin-2-one Hydrochloride (38a).—Dry HCl was passed into a suspension of 3 g of **35a** in 250 ml of methanol, the saturated solution was refluxed for 0.5 hr, and most of the excess reagent was removed *in vacuo*. The residue crystallized with the aid of ether and methanol, affording 2.9 g of colorless crystals: mp 195–197° dec, not raised on further recrystallization; ir 4.44 (moderate, broad), 5.21 (moderate to weak, broad) (immonium bands), 5.81, and 5.93 μ (shoulder 5.99 μ); uv 226 nm (ϵ 35,280), 285 (4930), and 350 (1230); nmr (D_2O) δ 8.6–7.5 (m, 8, ArH), 4.96 (m, 2, J_{AB} = *ca.* 12 Hz, methylene), 4.0 (s, 3, ester CH_3), and 3.93 (s, 3, NCH_3).

Anal. Calcd for $C_{18}H_{16}N_2O_3 \cdot HCl$: C, 62.70; H, 4.97; N, 8.12. Found: C, 62.37; H, 5.02; N, 8.00.

The corresponding **38a** base (imine), liberated from the salt with aqueous $NaHCO_3$, extracted with ether, and isolated by evaporation of the washed (water) and dried (K_2CO_3) solution, was a viscous, pale yellow glass: ir 5.78 and 5.96 μ (shoulders at 5.92 and 6.04 μ); uv 225 nm (ϵ 35,150) and inflections at 282 (2530) and 302 (1610); nmr ($CDCl_3$) δ 8.0–6.9 (m, 8, ArH), 4.34 (q, 2, J_{AB} = 12 Hz, methylene), 3.56 (s, 3, ester CH_3), and 3.51 (s, 3, NCH_3).

The imino acid corresponding to **38a** was obtained as the hydrochloride ethanolate as follows. A suspension of **35a** in *ca.* 50 parts of dry ether was saturated with dry HCl and let stand for 3 days. The crystals were collected and triturated, then recrystallized, with ethanol–ether as colorless crystals: mp 225–227.5° dec; readily soluble in water and dilute NaOH; ir broad, bonded OH band, 5.82–5.89 (broad ionic bands), and 6.06 μ; uv 225 nm (ϵ 39,120), 283 (5430), and 346 (1580); nmr (DMSO) had EtOH fingerprint.

Anal. Calcd for $C_{17}H_{14}N_2O_3 \cdot HCl \cdot C_2H_5OH$: C, 60.55; H, 5.62; N, 7.44. Found: C, 60.67; H, 5.63; N, 7.50.

Compound 38b Hydrochloride.—A sample (1.2 g) of **35b** in 200 ml of methanol was treated similarly with dry HCl. The yellow solution was either refluxed for 0.7 hr or let stand for 3 days. The residue, after evaporation and trituration with several portions of ether, crystallized in the presence of ether–methanol as 0.7 g of pale yellow crystals: mp 176–184° dec, raised to 191–193° dec on recrystallization from the same solvents; ir 4.50–5.18 (immonium), 5.82, and 5.95–6.08 μ; uv 227 nm (ϵ 41,250) and 312 (1980) with inflection at 284 (3180); nmr (DMSO) δ 8.5 (s, 1, D_2O exchange, HCl), 8.0–7.7 (m, 6, ArH), 6.88 (d, 1, proton 6), 4.3 (m, 2, methylene), 3.53 (s, 3, ester CH_3), and 3.43 (s, 3, NCH_3).

Anal. Calcd for $C_{18}H_{15}ClN_2O_3 \cdot HCl$: C, 57.00; H, 4.25; N, 7.39. Found: C, 56.67; H, 4.40; N, 7.32.

The base **38b**, like **38a**, was not crystalline, ir 5.83 and 5.94 μ.

2-Chloro-5-methyl-6,7-dihydro-13b-methoxyisoindolo[2,1-*d*][1,4]benzodiazepine-6,9-dione (37b).—Into a suspension of 1 g of **35b** in 40 ml of methanol was passed dry HCl just long enough to dissolve the crystals. On evaporation of the solution to smaller volume crystals of product separated, and were collected, washed with methanol, and dried, 0.75 g of colorless crystals, mp 211–214° dec. A sample, recrystallized from methanol, had mp 216–218.5° dec; ir 5.84 and 5.96 μ; uv 231 nm (ϵ 14,460) and 251 (15,340); nmr (DMSO) δ 8.0–7.6 (m, 6, ArH), 6.96 (s, 1, proton 1), 4.0 (q, 2, J_{AB} = 13 Hz, methylene), 3.33 (s, 3, OCH_3), and 2.86 (s, 3, NCH_3).

Anal. Calcd for $C_{18}H_{15}ClN_2O_3$: C, 63.07; H, 4.41; N, 8.17. Found: C, 63.16; H, 4.36; N, 8.19.

Alternatively, **37b** was prepared from **35b** using $SOCl_2$ followed by MeOH, as described in the next experiment.

Compound 37a.—A suspension of 2 g of **35a** in *ca.* 20 ml of $SOCl_2$ was warmed to reflux on a stream cone for *ca.* 5 min, or long enough to convert the reddish mixture to a light pink solution. The excess reagent was removed *in vacuo*, and the residue was treated immediately with methanol (*ca.* 40 ml). After the solution was warmed gently for a few minutes, the product crystallized directly from the warm solution, and was collected, washed with methanol and dried: yield 1.5 g of colorless crystals, mp 213–215° dec, raised on recrystallization from methanol to 236–237.5° dec; ir 5.84 and 5.97 μ; uv 231 nm (ϵ 15,340) and 246 (12,400); nmr ($CDCl_3$) δ 8.1–6.9 (m, 8, ArH), 4.12 (q, 2, J_{AB} = 12.5 Hz, methylene), 3.46 (s, 3, OCH_3), and 2.97 (s, 3, NCH_3).

Anal. Calcd for $C_{18}H_{16}N_2O_3$: C, 70.11; H, 5.35; N, 9.09. Found: C, 70.16; H, 5.18; N, 8.98.

Attempts to isolate the intermediate 13b-chloro compound in crystalline form were not successful.

1-Methyl-3-phenylindole-2-carbonitrile-2′-carboxylic Acid (36a) (R = H).—Crude **33a** (21 g) was treated with a solution of 4.3 g of Na in 300 ml of methanol, and the solution was refluxed for 1.6 hr. Most of the methanol was removed by distillation *in vacuo*, the residue was dissolved in water and the filtered solution was acidified with dilute HCl, and the product was collected, washed with water, and air dried, 17.5 g (93%), mp 200–202°. Recrystallization from aqueous ethanol and benzene gave pale yellow crystals: mp 198–200°; ir 4.48 (moderate to

intense) and 5.88 μ; uv 224 nm (ε 36,400) and 290 (14,450), inflection at 310 (4710).

Anal. Calcd for $C_{17}H_{12}N_2O_2$: C, 73.90; H, 4.38; N, 10.14. Found: C, 74.03; H, 4.57; N, 9.83.

Acid 36b (R = H) was prepared similarly from **33b** with methanolic $NaOCH_3$ (refluxed 3 hr) in a yield of 84%, mp 235–240°. Recrystallization from aqueous ethanol gave bright yellow crystals: mp 241–243°; ir 4.48 (moderate to intense) and 5.91 μ; uv 233 nm (ε 41,910), 296 (13680), and 321 (8610).

Anal. Calcd for $C_{17}H_{11}ClN_2O_2$: C, 65.70; H, 3.57; N, 9.02. Found: C, 65.51; H, 3.60; N, 9.13.

3-(2′-Carbomethoxyphenyl)-1-methylindole-2-carbonitrile (36a) (R = CH_3).—Solution of 17.5 g of **36a** (R = H) in 1 l. of saturated methanolic HCl was let stand for 2 days, the excess reagent was distilled *in vacuo*, and the crystals were collected, 17.8 g (96%) of pale yellow needles, mp, 162–165°, giving colorless needles, mp 165–166° on recrystallization from methanol: ir 4.46 (strong) and 5.82 μ; uv 222 nm (ε 37,190) and 290 (13,990); nmr ($CDCl_3$) δ 8.2–7.0 (m, 8, ArH), 3.86 (s, 3, ester CH_3), and 3.62 (s, 3, NCH_3).

Anal. Calcd for $C_{18}H_{14}N_2O_2$: C, 74.47; H, 4.86; N, 9.65. Found: C, 74.72; H, 5.00; N, 9.52.

Ester 36b (R = CH_3), prepared similarly from **36b** (R = H) in 94% yield, had mp 178.5–180° after recrystallization from ethanol; ir 4.47 (strong) and 5.77 μ; uv 233 (ε 43,250), 293 (13,490), and 322 (8720); nmr ($CDCl_3$) δ 8.1–7.4 (m, 7, ArH), 3.98 (s, 3, ester CH_3), and 3.63 (s, 3, NCH_3).

Anal. Calcd for $C_{18}H_{13}ClN_2O_2$: C, 66.57; H, 4.03; N, 8.63. Found: C, 66.64; H, 4.20; N, 8.62.

Dicarboxylic acid corresponding to **36a** was obtained *via* a diester corresponding to **33a**, as follows.

A. Esterification.—A solution of 1.9 g of **33a** in 50 ml of saturated, methanolic HCl was let stand for 5 days; after distillation of the methanol and addition of water, the neutral product was isolated as usual as an oil, ir 5.79 (intense) and 6.03 μ, uv 238 nm (ε 19,420) and 382 (3050).

B. Closure to Indole.—Crude A (0.9 g) with a solution of 0.2 g of Na in 30 ml of methanol was refluxed for 1.5 hr and the acidic product (**36a**, R = H; COOH and COOMe in place of CN) was isolated as described for **36a** (R = H) as 0.7 g of pale yellow solid, mp 212–215° dec, consisting of a mixture of diacid and acid ester. The latter could be separated by means of ether and recrystallized from the same solvent as crystals: mp 172–175°; ir 3.04, 5.81, and 5.96 μ; uv 223 nm (ε 30,910) and 296 (14,600), inflection at 316 (8960).

C. Hydrolysis of crude B by 3-hr reflux with 20 ml of 20% NaOH and acidification of the diluted, filtered solution gave the diacid as crystals from aqueous ethanol: mp 249–251° dec; ir 5.90 and 5.97–6.00 μ; uv 220 nm (ε 37,220) and 294 (14,120); nmr (DMSO) δ 12.5 (broad, 2, D_2O exchange, both COOH), 8.0–7.0 (m, 8, ArH), and 4.02 (s, 3, NCH_3).

Anal. Calcd for $C_{17}H_{13}NO_4$: C, 69.14; H, 4.44; N, 4.74. Found: C, 68.89; H, 4.54; N, 5.06.

2-Chloro-5-methylindolo[2,3-*d*][2]benzazepin-8(6*H*)-one (39b).—Owing to low solubilities of respective materials in alcohols, poor results were obtained in nickel reduction of ester nitriles **36** in amounts greater than a few grams in ethanolic ammonia and similar media. For larger scale work, therefore, the following procedure was used. A solution of 11.2 g of **36b** in 400 ml of NH_3-saturated glycol monoethyl ether (Cellosolve) and 50 ml of DMF, together with *ca.* 10 g of water- and alcohol-washed Grace 28 nickel catalyst, was shaken under H_2 (45 lb) at 50° for 8 hr, or until absorption ceased. The filtered solution on evaporation gave a crude residue from which 4.6 g of lactam **39b**, mp 301–303°, was isolated directly by trituration with ether. The oily residue remaining after evaporation of the filtrate was heated to 170° (oil bath) for *ca.* 15 min and cooled, and the solid was triturated with ether to give 4.1 g of additional lactam, bringing the yield of **39b** to 8.7 g (85%). Recrystallization from ethanol gave colorless needles: mp 310–312°; ir 3.03–3.10 (bonded), 6.09, and 6.21–6.26 μ; uv 234 nm (ε 38,380) and 275 (13,250) with inflections at 216 (30,060), 291 (10,830), and 304 nm (10,180).

Anal. Calcd for $C_{17}H_{13}ClN_2O$: C, 68.80; H, 4.41; N, 9.44. Found: C, 68.77; H, 4.42; N, 9.49.

In a similar reduction of **36b** (2 g) in ammoniacal DMF–ethanol (200 ml) at 30° there was isolated a fairly pure sample of the intermediate amino ester, **2-aminomethyl-3-(2′-carbomethoxyphenyl)-5-chloro-1-methylindole**, as colorless crystals (from ether): mp 98–100°; ir NH highly bonded, visible only in solution (chloroform) spectra, and 5.79 μ; uv 231 nm (ε 80,710) and 286 (17,700) with inflection at 304 (15,710); nmr ($CDCl_3$) δ 8.0–7.0 (m, 7, ArH), 3.81 (s, 2, methylene), 3.72 (s 3, ester CH_3), 3.52 (s, 3, NCH_3), and 1.24 (s, 2, D_2O exchange, NH_2).

Anal. Calcd for $C_{18}H_{17}ClN_2O_2$: C, 65.75; H, 5.21; N, 8.52. Found: C, 66.18; H, 5.51; N, 8.52.

When the NH_3 was omitted in a similar hydrogenation of 8.9 g of ester nitrile **36b**, there were obtained 2.3 g of lactam **39b** and from the ether filtrate 4.5 g of secondary amine, **bis[3-(2′-carbomethoxyphenyl)-5-chloro-1-methylindolyl-2-methyl]amine**, as colorless crystals from ethanol: mp 166–168°; ir 5.78 μ; uv 230 nm (ε 58,410) and 314 (27,670).

Anal. Calcd for $C_{36}H_{31}Cl_2N_3O_4$: C, 67.50; H, 4.88; N, 6.56. Found: C, 67.53; H, 4.56; N, 6.48.

Lactam 39a was obtained by similar nickel-catalyzed hydrogenation of **36a** in the presence of ammonia in alcohol, DMF, or cellosolve, and thermal closure of crude, intermediate amino ester. Recrystallization from ethanol afforded colorless crystals: mp 309–311°; ir 3.12 (broad, weak), 6.07, and 6.21 μ; uv 227 nm (ε 36,660), 274 (11,130), and 284 (10,920) with inflection at 215 (30,740); nmr (DMSO) δ 8.5–7.0 (m, 9, 1 D_2O exchange, ArH and NH), 4.22 (d, 2, $J \cong 6$ Hz, collapse to s on D_2O exchange of NH, methylene), and 3.8 (s, 3, NCH_3).

Anal. Calcd for $C_{17}H_{14}N_2O$: C, 77.84; H, 5.38; N, 10.68. Found: C, 77.20; H, 5.62; N, 10.33.

When nickel-catalyzed hydrogenation of **36a** (21 g) was carried out in DMF, omitting the NH_3, the crude product contained *ca.* 3 g of lactam **39a** and the remainder of the material was a mixture of basic esters and partly reduced substance (imine), ir 5.80–5.83 and 6.14 μ. Treatment of the crude solid with 30% aqueous HCl and recrystallization of the resulting, water-washed, crude crystals from ether and ethanol gave **3-(2′-carbomethoxyphenyl)-1-methylindole-2-carboxaldehyde**: mp 117–119°; ir 5.80 and 6.00 μ; uv 227 nm (ε 21,490) and 314 (18,420) with inflection at 350 (7110); nmr ($CDCl_3$) δ 9.7 (s, 1, CHO), 8.2–7.0 (m, 8, ArH), 4.16 (s, 3, ester CH_3), and 3.54 (s, 3, NCH_3).

Anal. Calcd for $C_{18}H_{15}NO_3$: C, 73.70; H, 5.15; N, 4.78. Found: C, 74.01; H, 5.28; N, 5.10.

***N*-Methyl Lactam 39c (X = H).**—Lactam **39a** (3 g) was added to 0.85 g of 56% NaH in 10 ml of DMF, and the red, effervescent mixture was treated with 2 ml of iodomethane. When the exothermic reaction subsided, 2 ml of additional CH_3I was added and the suspension was stirred for 3 hr. Water was added, and the crude product (3 g) was collected, washed with water, air dried, and triturated with ether to give 2.0 g of crystals: mp 251–253°, raised to 253–255° on recrystallization from ethanol; ir 6.19 μ; uv 215 nm (ε 30,020), 228 (36,950), 271 (11,460), 282 (10,730) and 291 (10,630); nmr (DMSO) δ 7.9–7.0 (m, 8, ArH), 4.46 (s, 2, methylene), 3.88 (s, 3, indole NCH_3), and 3.13 (s, 3, lactam NCH_3).

Anal. Calcd for $C_{18}H_{16}N_2O$: C, 78.23; H, 5.84; N, 10.14. Found: C, 78.55; H, 5.71; N, 10.23.

***N*-Methyl Lactam 39c (X = Cl).**—Similar methylation of **39b** in the presence of NaH afforded colorless crystals (from DMF–ethanol): mp 315–316°; ir 6.21 μ; uv 234 nm (ε 38,600), 274 (13,490), 290 (10,460), and 303 (10,440).

Anal. Calcd for $C_{18}H_{15}ClN_2O$: C, 69.56; H, 4.87; N, 9.02. Found: C, 69.48; H, 4.85; N, 8.96.

Lactam 39d (X = Cl, *n* = 2).—To 3.0 g of **39b** in 30 ml of DMSO was added 1.5 g of potassium *tert*-butoxide, then 20 ml of 1.8 *M* solution of β-dimethylaminoethyl chloride in toluene. The mixture was stirred for 6 hr at *ca* 75°; 5 ml additional chlorodimethylaminoethane reagent was added; and the mixture was let stand for 1–2 days. After addition of water, a benzene extract of crude material was washed (three portions of water), dried (K_2CO_3), and evaporated. Trituration of the crude residue with ether gave 1.5 g of crystals: mp 224–225° before and after recrystallization (EtOH); ir 6.18 μ; uv 235 nm (ε 38,720), 275 (13,680), 290 (10,500), and 301 (10,310); nmr ($CDCl_3$) δ 8.1–7.1 (m, 7, ArH), 4.4 (s, 2, lactam methylene), 3.78 (s, 3, indole NCH_3), 3.70 (t, 2, $J = 7$ Hz, chain CH_2 attached to lactam N), 2.48 (t, 2, $J = 7$ Hz, methylene adjacent to NMe_2), and 2.2 (s, 6, NMe_2).

Anal. Calcd for $C_{21}H_{22}ClN_3O$: C, 68.56; H, 6.03; N, 11.42. Found: C, 68.58; H, 5.97; N, 11.62.

Lactam 39d (X = Cl, *n* = 3).—Similar potassium *tert*-butoxide mediated alkylation of **39b** with 1-chloro-3-dimethylaminopropane gave, after recrystallization from benzene, crystals, mp 180–181°, ir 6.18–6.25 μ, uv and nmr like those of the preceding compound.

Anal. Calcd for $C_{22}H_{24}ClN_3O$: C, 69.19; H, 6.33; N, 11.00. Found: C, 69.30; H, 6.40; N, 10.77.

Alkylation of **39a** and **b** with basic halides in the presence of NaH was less satisfactory.

Registry No.—**1b** amidoxime 2HCl, 36271-17-7; **1c**, 36271-18-8; **1d**, 36271-19-9; **1e**, 36208-00-1; **1e** amidoxime, 36271-20-2; **2a** HCl, 36271-21-3; **2b** HCl, 36271-22-4; **2c** 2HCl, 36271-23-5; **2e** 2HCl, 36271-24-6; **4a**, 36271-25-7; **4b**, 36271-26-8; **4c**, 36271-27-9; **4d**, 36271-28-0; **4e**, 36271-29-1; **5a**, 36271-30-4; **5a** HCl, 36271-31-5; **5b**, 36271-32-6; **5b** HCl, 36271-33-7; **5c** HCl, 36271-34-8; **5e** HCl, 36271-35-9; **6**, 36271-36-0; **6** HCl, 36271-37-1; **8b**, 36258-91-0; **9b**, 36258-92-1; **11**, 36207-97-3; **12a**, 36270-92-5; **12b**, 36270-93-6; **13**, 36270-94-7; **14**, 36270-95-8; **16**, 4015-28-5; **16** dihydro formic acid salt, 36270-97-0; **17**, 36270-98-1; **18a**, 36270-99-2; **18b**, 36271-00-8; **18c**, 10456-63-0; **18d**, 36271-02-0; **19**, 36207-98-4; **21b**, 36271-03-1; **22**, 36271-04-2; **23**, 1022-13-5; **24**, 36271-06-4; **24** amide, 36271-07-5; **25**, 2898-12-6; **25** HCl, 2898-11-5; **26a**, 24139-18-2; **26b** HCl, 36271-11-1; **26c** HCl, 21139-23-1; **26d**, 21139-24-2; **28b**, 3311-40-8; **28c**, 16219-18-4; **28d**, 36271-15-5; **28e**, 36271-16-6; **29a** (R′ = CH_3), 36259-21-9; **29b** (R′ = H), 36259-22-0; **29b** (R′ = H) *N*-chloroacetyl derivative, 36259-23-1; **29b** (R′ = H) HBr, 36259-24-2; **29b** (R′ = CH_3), 36259-25-3; **29c** (R′ = H), 16175-35-2; **29c** (R′ = CH_3), 36259-27-5; **29d** (R′ = H), 36259-28-6; **29e** (R′ = H), 36259-29-7; **29e** (R′ = CH_3), 36259-30-0; **30c**, 36208-04-5; **31**, 36259-31-1; **32a** (R′ = CH_3), 36259-32-2; **32b** (R′ = H), 36259-33-3; **32b** (R′ = CH_3), 36259-34-4; **33b**, 36259-35-5; **34a**, 36259-36-6; **34b**, 36258-42-1; **35a**, 36258-43-2; **35b**, 36258-44-3; **35c**, 36258-45-4; **35d**, 36258-46-5; **36a** (R = H), 36258-47-6; **36a** (R = CH_3), 36258-48-7; **36a** dicarboxylic acid, 36258-49-8; **36b** (R = H), 36258-50-1; **36b** (R = CH_3), 36258-51-2; **37a**, 36258-52-3; **37b**, 36258-53-4; **38a**, 36208-05-6; **38a** HCl, 36258-54-5; **38a** imino acid HCl, 36258-55-6; **38b** HCl, 36258-56-7; **39a**, 36258-57-8; **39b**, 36258-58-9; **39c** (X = H), 36258-59-0; **39c** (X = Cl), 36258-60-3; **39d** (X = Cl, n = 2), 36258-61-4; **39d** (X = Cl, n = 3), 36258-62-5; i, 36258-63-6; *p*-chloroanilinoacetonitrile, 24889-92-7; *p*-chloroanilinoacetamide, 21979-12-4; *N*-acetyl-*p*-chloroanilinoacetonitrile, 36258-66-9; *p*-chloro-*N*-acetylanilinoacetonitrile amidoxime, 36258-67-0; 4-*N*-benzylideneaminoveratrale, 13548-24-8; 2,3-dimethoxy-6,7,9,13b-tetrahydroisoindolo[2,1-*d*][1,4]benzodiazepine HCl, 36258-69-2; 2-(α-hydroxybenzyl)-4-chloroanilinoacetonitrile, 36258-70-5; 6-chloro-1,2-dihydro-2,2-dimethylquinazoline 3-oxide, 4844-66-0; *N*-(2-aminoethyl)-*N*-methyl-2-benzoyl-4-chloroaniline hydrochloride, 36258-72-7; 6,7-dihydro-13b-hydroxyisoindolo[2,1-*d*][1,4]benzodiazepine-6,9-dione, 36258-73-8; 6,7-dihydroisoindolo[2,1-*d*][1,4]benzodiazepine-6,9-dione, 36258-74-9; 5-methyl-6,7-dihydroisoindolo[2,1-*d*][1,4]benzodiazepine-6,9(13b*H*)-dione, 36258-75-0; 2-aminomethyl-3-(2′-carbomethoxyphenyl)-5-chloro-1-methylindole, 36258-76-1; bis[3-(2′-carbomethoxyphenyl)-5-chloro-1-methylindolyl-2-methyl]amine, 36258-77-2; 3-(2′-carbomethoxyphenyl)-1-methylindole-2-carboxaldehyde, 36258-78-3; *N*-methyl-*m*-methoxyacetanilide, 36258-79-4.

Acknowledgment.—We are indebted to Mr. George Robertson, Mr. Rudolf Oeckinghaus, Miss Natalie Cahoon, Mr. Charles Navarro, Mr. Mike Hotolski, Mr. Anis Hamden, and Miss Barbara Biffar of the staff of Mr. Louis Dorfman for microanalytical and spectral data, to Mr. Robert Dziemian and Miss Ann Smith for large-scale preparation of certain intermediates, to Mrs. Angela Aretakis and Dr. John Marsh for some literature search work, and especially to Miss Ruth Behnke for precise nmr spectra and their interpretation. Discussion of various phases of the effort with Dr. Neville Finch is cordially acknowledged.

Heterocyclic Studies. 37. Rearrangements of a Dihydro-1,2-diazepin-4-ol and 1,2-Diazabicyclo[3.2.0]hepten-6-ol to a Tetrahydropyridazine

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Received June 19, 1972

Acylation of diazepinol **1** in the presence of weak organic bases gives the oxides **2**; the bicyclo[3.2.0]alcohols **3** rearrange to **2**, but are not intermediates in the conversion **1** → **2**. With triethylamine, acylation of **1** gives the 4-formyltetrahydropyridazines **5**, which are also obtained by thermal rearrangement of **3**. The tetrahydropyridazines are converted by successive oxidation and deacylation to 4-methyl-5-phenylpyridazine (**9**). The reaction of **1** and **3** are suggested to occur *via* an acyldiazepinium cation–acylbetaine system (**10–12**).

The preparation and interconversion of the diazepinol **1**, bicyclo[3.2.0] alcohol **3a**, and bridged oxide **2a** were reported some time ago.[1] The bicyclic alcohol **3a**, obtained by reduction of the corresponding ketone, is converted by mild acid to the oxide **2a**; the latter is also produced by acetylation of **1**. The noncrystalline acetate ester of **3a** was obtained in impure form by acetylation of **1** in the presence of pyridine, and **3a** was suggested as an intermediate in the conversion of **1** to **2**. A terminal acid-catalyzed elimination leads from **2** or **3** to furfurylhydrazine derivatives **4**. Further work in this series has extended our understanding of these reactions and has revealed an important rearrangement process which was missed in the earlier work.

To provide more complete characterization of the [3.2.0] bicyclic alcohols, the *N*-benzoyl alcohol **3b** was prepared and converted to the crystalline acetate and benzoate esters. As in the acetyl series, a single epimeric alcohol was produced in the reduction of the benzoyl[3.2.0] ketone; the hydroxyl configuration is assumed to be endo from the expected exo attack of

(1) J. A. Moore, R. W. Medeiros, and R. L. Williams, *J. Org. Chem.*, **31**, 52 (1966).