Heterocyclic Syntheses from o-Aminonitriles. XXX. Synthesis of Some Diaza Steroids[1]

EDWARD C. TAYLOR AND YOUVAL SHVO[2]

Department of Chemistry, Princeton University, Princeton, New Jersey 08540

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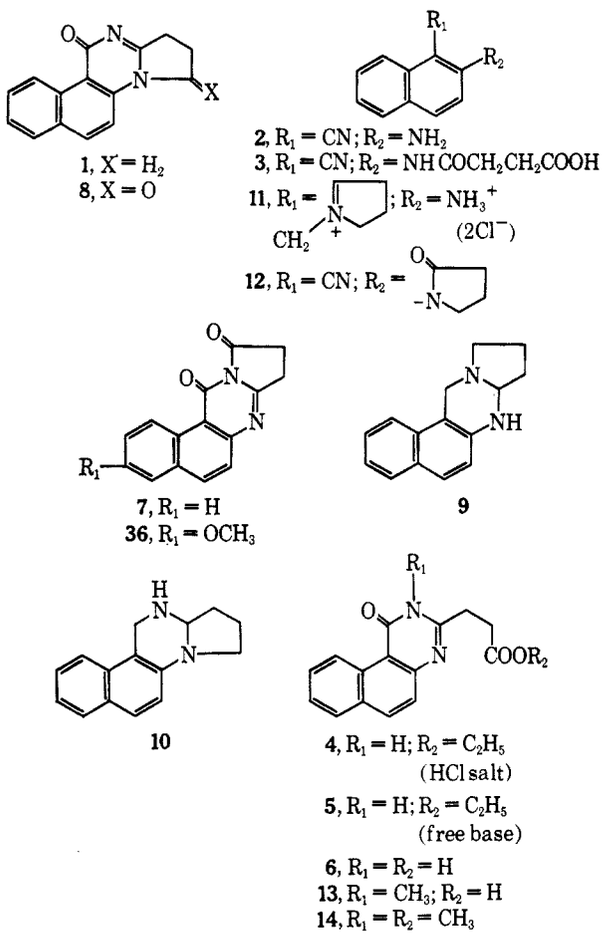
1-Cyano-2-naphthylamine has been converted into 8,9-dihydrobenzo[*f*]pyrrolo[2,1-*b*]quinazoline-10,12-dione (**7**) in four steps, and to 2,3-dihydrobenzo[*f*]pyrrolo[1,2-*a*]quinazolin-11(1H)-one (**1**) in two steps. 1-Cyano-6-methoxy-2-naphthylamine has been converted into 2,3-dihydro-8-methoxybenzo[*f*]pyrrolo[1,2-*a*]quinazolin-11(1H)-one (**39**) in three steps. 2,3-Dihydropyrrolo[1,2-*a*]quinazolin-9(1H)-one (**27**), a tricyclic model of **39**, was prepared from anthranilonitrile. A number of transformations of **39** and **27** are reported which reflect the active methylene character of the $-CH_2-$ grouping at position 1 (C-17 by steroid numbering). A modified Mannich reaction is described which results in the direct synthesis of olefins which are usually obtained by the pyrolysis of preformed Mannich bases.

There has been considerable recent concern with the preparation of synthetic steroid derivatives in which a nitrogen atom has replaced one of the skeletal carbons of the steroid nucleus[3] (these are true aza steroids, as contrasted to normal steroidal derivatives in which a nitrogen has been incorporated either into a side chain or into an extra ring).[4] We describe in the present paper the total synthesis of a number of derivatives of a new diaza steroid system, 2,3-dihydrobenzo[*f*]pyrrolo-[1,2-*a*]quinazolin-11(1H)-one (**1**).

Fusion of 1-cyano-2-naphthylamine (**2**)[5] with freshly prepared succinic anhydride gave **3** in 84% yield. Although this reaction could alternately be carried out by heating the reactants together in solvents such as benzene or toluene, simple fusion proved both to be more convenient and to lead to substantially higher yields of **3**. Treatment of this latter compound with dry hydrogen chloride in anhydrous ethanol then resulted in the separation of the colorless crystalline hydrochloride of ethyl β-(1,2-dihydro-1-oxobenzo[*f*]quinazolin-3-yl)propionate (**4**). The major by-product in this acid-catalyzed cyclization was the initial aminonitrile **2** which does not, however, form a hydrochloride salt and is thus soluble in the reaction medium. The crystalline free base **5** was obtained by hydrolysis of **4** with water, while the acid **6** was most conveniently obtained in yields in excess of 95% by alkaline hydrolysis of the hydrochloride ester **4**.

Our hope at this point was to effect a dehydrative cyclization of **6** in a manner analogous to previously described cyclodehydrations of β-quinoxalinylpropanoic acids to pyrrolo[1,2-*a*]quinoxalinones.[6,7] When the propanoic acid **6** was heated with a mixture of acetic anhydride and toluene, an intramolecular dehydration product $C_{15}H_{10}N_2O_4$ was obtained in 90% yield. This product must possess either structure **7** or **8**. Although the nmr spectrum of the cyclodehydration product was consistent with either structure, chemical degradation firmly established that the product was in fact 8,9-dihydrobenzo[*f*]pyrrolo[2,1-*b*]quinazoline-10,12-dione (**7**). Thus, reduction of the cyclization product (**7** or **8**) with diborane in tetrahydrofuran, followed by acid hydrolysis of the reaction mixture, gave an oil in 40–50% yield which no longer contained a carbonyl group (ir spectrum) and which showed only one broad unresolved NH stretching band. Its nmr spectrum showed a singlet at 4.2 (two benzylic protons) and a triplet at 4.1 ppm, integrating to one proton, which must be the tertiary aminal proton of either **9** or **10**. These observations confirm that complete reduction of the cyclodehydration



product (**7** or **8**) had taken place without concurrent fission of the carbon skeleton. Although the evidence cited thus far is consistent with either **9** or **10**, the observation that the diborane reduction product, upon treatment with sodium nitrite in dilute hydrochloric acid, gave a diazonium salt which coupled with β-naphthol to yield a bright orange azo dye, firmly established its structure as 7,7a,8,9,10,12-hexahydrobenzo[*f*]pyrrolo-[2,1-*b*]quinazoline (**9**). Only this latter compound (and

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(2) On leave from the Weizmann Institute of Science, Rehovoth, Israel; currently at Tel-Aviv University, Ramat-Aviv, Tel-Aviv, Israel.

(3) For a bibliography of recent references, see R. E. Brown, D. M. Lustgarten, R. J. Stanaback, and R. I. Meltzer, *J. Org. Chem.*, **31**, 1489 (1966).

(4) C. W. Shoppee, "Chemistry of the Steroids," 2nd ed, Butterworth, Inc., Washington, D. C., 1964, pp 433–463.

(5) H. Bretschneider and K. Hohenloh-Oehringen, *Monatsh.*, **89**, 358 (1958).

(6) E. C. Taylor and E. S. Hand, *J. Amer. Chem. Soc.*, **85**, 770 (1963).

(7) E. C. Taylor and G. W. H. Cheeseman, *ibid.*, **86**, 1830 (1964).

TABLE I

ULTRAVIOLET ABSORPTION DATA

Compd	Solvent	λ_{max}, mμ (ε)								
1	Ethanol	352 (6,060)	345 (s) (4,420)	336 (5,600)	323 (3,500)	296 (9,560)	273 (53,600)	264 (45,200)	244 (16,300)	
5	THF	349 (6,150)	343 (3,337)	334 (5,570)	320 (5,800)	298 (7,050)	286 (7,330)	272 (38,400)	263 (42,500)	255 (35,200)
7	THF	357 (6,260)	351 (s) (4,820)	342 (8,000)	325 (8,070)	311 (7,830)	278 (50,600)	266 (48,200)	256 (38,800)	244 (20,900)
14	THF	350 (5,200)	344 (3,000)	335 (4,600)	320 (3,100)	298 (7,060)	287 (6,600)	274 (32,200)	263 (33,900)	256 (23,400)
15	Ethanol	317 (7,000)	305 (8,400)	297 (s) (6,300)	275 (5,000)	265 (4,470)	229 (16,000)			
36	THF	373 (6,050)	352 (6,050)	340 (3,220)	307 (7,000)	280 (s) (29,400)	270 (44,000)	263 (s) (35,000)		
39	Ethanol	370 (5,700)	353 (5,720)	335 (3,900)	295 (9,900)	272 (39,000)	266 (s) (3,360)			
41	Ethanol	362 (4,200)	331 (2,200)	297 (11,800)	270 (44,800)	264 (47,200)				
42	Ethanol	365 (5,800)	348 (5,400)	324 (4,000)	295 (s) (16,000)	272 (53,000)	266 (51,000)			
43	Ethanol	368 (s) (7,300)	352 (s) (11,700)	334 (13,900)	285 (35,700)	279 (35,400)	255 (s) (25,400)	232 (24,600)		
44	Ethanol	353 (35,200)	305 (16,500)	274 (16,300)	264 (15,900)	246 (22,300)				
46	Ethanol	367 (7,200)	350 (9,700)	336 (10,000)	286 (30,000)	278 (30,000)	238 (34,000)			

not **10**) is capable of acid-catalyzed hydrolysis of the aminal linkage to give a primary aromatic amine (**11**).[8]

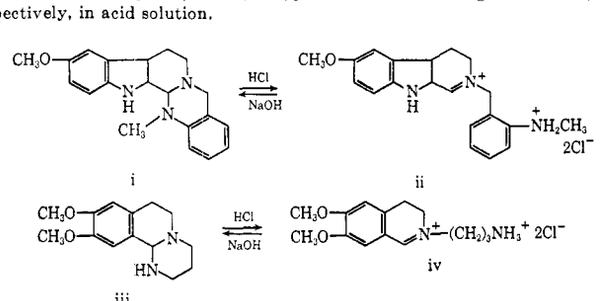
The cyclodehydration product **7** is an unusually reactive imide. It is converted in quantitative yield back into the ethyl ester **5** upon refluxing for 15 min in ethanol. Hot water converts it rapidly into the carboxylic acid **6**. The unusually high reactivity of this cyclic imide may be due in part to relief of carbonyl dipole–dipole interactions (which must be particularly high in the rigid 5,6-fused ring system found in **7**) in the transition state involved in hydrolysis.

Conversion of 1-cyano-2-naphthylamine (**2**) into **1** was finally accomplished in a surprisingly easy sequence as follows. Condensation of **2** with butyrolactone at elevated temperatures for extended periods of time gave N-(1-cyano-2-naphthyl)pyrrolidone (**12**) in 50% yield. The reaction was sluggish and results were erratic; the temperature required for reaction was close to the temperature of decomposition of the product and satisfactory reaction conditions were not found. However, treatment of the pyrrolidone **12** with dry hydrogen chloride in anhydrous ethanol resulted in cyclization to 2,3-dihydrobenzo[*f*]pyrrolo[1,2-*a*]quinazolin-11(1H)-one (**1**). In contrast to the lability of the cyclic imide **7**, the 1,2-disubstituted quinazolinone derivative **1** exhibited hydrolytic stability normal for compounds of this type (*vide infra*).[9-12]

As an independent, although by itself inconclusive, confirmation of the structure of **1**, its ultraviolet spectrum was shown to be somewhat different (particularly at shorter wavelengths) from the spectrum of methyl β-(2-methyl-1,2-dihydro-1-oxobenzo[*f*]quinazolin-3-yl)-propionate (**14**) (see Table I), prepared by dimethyl sulfate methylation of **6** in dilute sodium hydroxide. The structure of **14** was conclusively established by vigorous alkaline hydrolysis to 1-(N-methylcarbamoyl)-2-aminonaphthalene. This latter compound gave a positive diazo coupling reaction with β-naphthol, clearly distinguishing it from its possible isomer, 1-carbamoyl-2-methylaminonaphthalene, which would have been the cleavage product had methylation of **6** occurred on N_4 rather than N_2.

The diaza steroid **1** is a tetracyclic derivative of a 1,2-dialkylquinazolin-4(1H)-one, a simple but relatively unknown[9-11] type of quinazoline derivative. In order to gain some insight into the probable chemical reactivity of **1**, 1,2-dimethylquinazolin-4(1H)-one (**15**) was prepared and some of its chemical reactions were studied, with particular interest centered on the reactivity of the 2-methyl group as a model of the anticipated active methylene position (C-17 by steroid numbering) of **1**. Methylation of N-acetylanthranilonitrile (**16**) with dimethyl sulfate in aqueous sodium hydroxide gave N-methyl-N-acetylanthranilonitrile (**17**) which was cyclized in anhydrous ethanol with dry hydrogen chloride to give the hydrochloride of **15**, from which the free base was liberated with aqueous sodium acetate. This

(8) The structure of **10** in acid solution is suggested as **11** by analogy with the known behavior of dihydrodesoxohortiamine (i) [I. J. Pachter, R. J. Mohrbacher, and D. E. Zacharias, *ibid.*, **88**, 635 (1961)] and 9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11b-pyrimido[2,1-*a*]isoquinoline (iii) [T. Yamazaki, *J. Pharm. Soc. Jap.*, **79**, 1014 (1959)] which are known to give ii and iv, respectively, in acid solution.

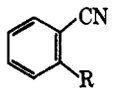


(9) A. Weddige, *J. Prakt. Chem.*, [2] **36**, 152 (1887).

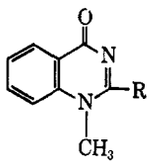
(10) I. M. Heilbron, F. N. Kitchen, E. B. Parkes, and G. D. Sutton, *J. Chem. Soc.*, **127**, 2167 (1925).

(11) D. Chakravarti, R. N. Chakravarti, L. A. Cohen, B. Dasgupta, S. Datta, and H. K. Miller, *Tetrahedron*, **16**, 224 (1961).

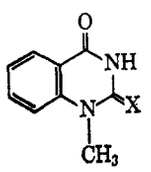
(12) H. M. Blatter, H. Lukaszewski, and G. deStevens, *J. Org. Chem.*, **30**, 1020 (1965).



16, R = $NHCOCH_3$
17, R = $N(CH_3)COCH_3$



15, R = CH_3
18, R = $CH_2CH(OH)CCl_3$
19a, R = $CH{=}C(OH)CH_3$
b, R = CH_2COCH_3
20a, R = $CH{=}C(OH)C_6H_5$
b, R = $CH_2COC_6H_5$
23, R = $CH{=}CHC_6H_5$



19, X = $CHCOCH_3$
20, X = $CHCOC_6H_5$
21, X = $C(COCF_3)_2$
22, X = $CHCOCO_2C_2H_5$

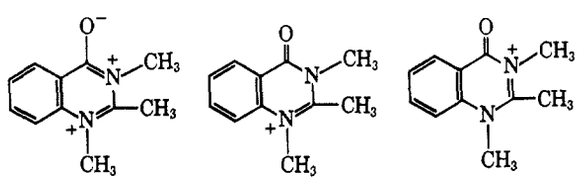
simple route to 1,2-dimethylquinazolin-4(1H)-one (**15**) constitutes a substantial improvement over previously recorded procedures for its preparation.[9-10]

The 2-methyl substituent of **15** underwent reactions typical of an active methylene group. It formed a chloral adduct **18** in excellent yield; acetylation yielded a monoacetyl derivative **19**. The constitution of this latter product is of some intrinsic interest. Its infrared spectrum indicated a carbonyl stretching band at 1680 cm^{-1} where the very low frequency may be attributed to the combined effects of α,β unsaturation and to intramolecular hydrogen bonding. Its nmr spectrum (CF_3CO_2H) indicated two different methyl signals and a broad band at 4.0 ppm (integration two protons) which disappeared at higher temperatures and reappeared upon cooling. This behavior, characteristic of proton exchange in acid solution, probably involves the process **19** $\rightleftarrows$ **19a** $\rightleftarrows$ **19b**. The monoacetyl derivative **19** gave a positive ferric chloride test; similar behavior has been observed in an analogous system by Blatter, *et al.*[12] Reaction of **15** with benzoyl chloride in pyridine gave a monobenzoyl derivative (**20**) with properties analogous to those exhibited by the monoacetyl derivative **19**. Acylation with trifluoroacetic anhydride gave a quantitative yield of a bis(trifluoroacetyl) derivative (**21**).

Analogous active methylene character in the 2-methyl group of **15** was exhibited in its reaction with diethyl oxalate in the presence of sodium ethoxide. A monoethoxalyl derivative **22** was obtained whose nmr spectrum indicated the presence of a single ethoxyl grouping, an N-methyl group and a signal at 6.33 ppm (integration one proton) which disappeared upon raising the temperature and reappeared upon cooling to room temperature. Its infrared spectrum exhibited an ester carbonyl stretching band at 1725 and a double intensity for the resolved band at 1705 cm^{-1} probably due to the remaining two carbonyl groupings in the molecule. Both bands are low, however, for nonconjugated α-keto esters and it may therefore be assumed that, as in the acetyl and benzoyl compounds (**19** and **20**, respectively), intramolecular hydrogen bonding favors a structure in which the side-chain carbonyl is conjugated directly to the ring (*i.e.*, structure **22**).

We confirm the report that **15** forms a benzylidene derivative (**23**) with benzaldehyde.[10] Reaction with formaldehyde under various conditions led only to resins. Compound **15** was recovered unchanged upon attempted nitrosation with isoamyl nitrite in the presence of sodium methoxide.

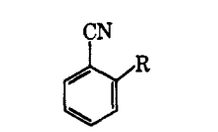
The reaction of **15** with methyl iodide is apparently self-catalyzed (no alkali is required) and gives a monomethiodide. Although there are four possible sites for methylation (N_1, C_2–CH_3, N_3, or the oxygen at position 4), the product was shown to be 1,2,3-trimethyl-4-oxoquinazolinium iodide (**24a**, **b**, and **c**) by examination of its nmr spectrum, which showed two separate and unsplit N-methyl groups (3.84 and 3.55 ppm) and one C-methyl signal. Furthermore, the infrared spectrum of the product showed a carbonyl band at 1710 cm^{-1} thus firmly excluding oxygen methylation. The unusually high frequency of this amide carbonyl band as compared with the starting material **15** (1625 cm^{-1}) can be rationalized in terms of the resonance structures **24a**, **b**, and **c**. Resonance form **24a**, which contributes to the



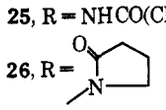
24a **24b** **24c**

lowering of the carbonyl frequency in amides, would be decreased in **24** in view of contributing structures such as **24c**. This situation is thus analogous to that existing in amides.

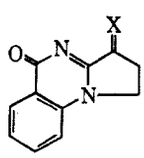
Although **15** appeared to be a valid model for the diaza steroid system **1**, with the C_2-methyl group simulating the anticipated activity of the C_1- (C_{17} steroid numbering) methylene group in the latter, a few additional experiments were carried out with a related model, 2,3-dihydropyrrolo[1,2-*a*]quinazolin-9-(1H)-one (**27**), which represents rings B, C, and D of **1** in their entirety. Condensation of anthranilonitrile with 4-chlorobutyryl chloride gave the amide **25** in quantitative yield, and this was converted into the pyrrolidone **26** with sodium hydroxide in aqueous methanol at room temperature. Cyclization to **27** was then effected in quantitative yield using dry hydrogen chloride in absolute ethanol. Treatment of **27** with isoamyl nitrite gave the oxime **28**, while reaction with bis(dimethylamino)methane in acetic anhydride gave the exomethylene derivative **29** (*vide infra.*)



25, R = $NHCO(CH_2)_3Cl$

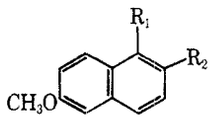


26, R =

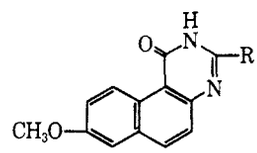


27, X = H_2
28, X = NOH
29, X = CH_2

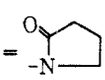
Having thus established, through a study of **15** and **27**, that chemical modifications at the C_1-active methylene position were readily accomplished, the tetracyclic diaza steroid 2,3-dihydro-8-methoxybenzo[*f*]pyrrolo-[1,2-*a*]quinazolin-11(1H)-one (**39**) (the 8-methoxy derivative of **1**) was prepared as follows. 6-Methoxy-2-naphthylamine (**30**)[13] was brominated in glacial acetic acid, and the crude bromination product acetylated with acetic anhydride in pyridine. Recrystallization of the acetylated product then yielded an ethanol-insoluble dibromo compound, probably 1,5-dibromo-6-methoxy-2-acetamidonaphthalene (**31**), and an ethanol-soluble monobromo compound (**32**). The structure of the

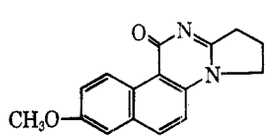


30, $R_1 = H$, $R_2 = NH_2$
32, $R_1 = Br$; $R_2 = NHCOCH_3$
33, $R_1 = CN$; $R_2 = NHCOCH_3$
35, $R_1 = CN$; $R_2 = NH_2$
37, $R_1 = CN$; $R_2 = NHCOCH_2CH_2CH_2Cl$



34, $R = CH_3$
40, $R = CH_2CH_2CH_2Cl$

38; $R_1 = CN$; $R_2 =$ 



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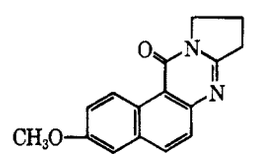


41

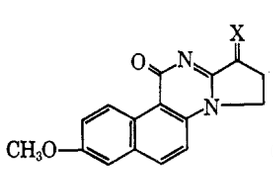
latter was confirmed by reaction with cuprous cyanide in anhydrous pyridine to give 1-cyano-2-acetamido-6-methoxynaphthalene (**33**), which was converted into 3-methyl-8-methoxybenzo[*h*]quinazolin-1(2H)-one (**34**) by treatment with dry hydrogen chloride in anhydrous ethanol. This sequence of conversions places the cyano group in **33** *ortho* to the acetamido grouping and consequently establishes the structure of the parent monobromo compound as **32**.[14]

Aqueous alkaline hydrolysis of **33** gave 1-cyano-6-methoxy-2-naphthylamine (**35**) which was converted into the cyclic imide **36** by fusion with succinic anhydride, cyclization to the quinazolinone with dry hydrogen chloride in anhydrous ethanol, hydrolysis, and cyclodehydration with acetic anhydride in refluxing toluene. The properties of this product (**36**) were analogous to those previously observed for **7**.

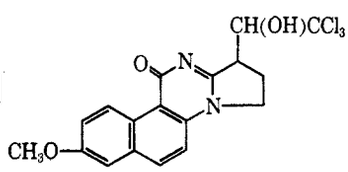
Attempted reaction of **35** with butyrolactone, in a reaction patterned after the successful conversion of **2** into **12** discussed above, proved to be unsuccessful. At lower temperatures only starting material was recovered, but at higher temperatures total decomposition ensued. These results are surprising, since introduction of a methoxyl grouping at position 6 should have increased the nucleophilicity of the 2-amino grouping. However, the desired pyrrolidone **38** was prepared by the reaction of 1-cyano-6-methoxy-2-naphthylamine (**35**) with 4-chlorobutyryl chloride to give 4-chloro-N-(1-cyano-6-methoxy-2-naphthyl)butyramide (**37**) which was cyclized to **38** with sodium methoxide in ethanol. Subsequent reaction of the pyrrolidone **38** with dry hydrogen chloride in anhydrous ethanol resulted in smooth cyclization to the desired diaza steroid **39**.

When the order of the above reactions was reversed, *i.e.*, when **37** was first treated with dry hydrogen chloride in anhydrous ethanol, 3-(3-chloropropyl)-8-methoxybenzo[*h*]quinazolin-1(2H)-one (**40**) was obtained, which with sodium methoxide in ethanol yielded two isomeric cyclization products. One proved to be identical with the product obtained by cyclization of **38**, whereas the other has been assigned the isomeric structure of 9,10-dihydro-3-methoxybenzo[*f*]pyrrolo-[2,1-*b*]quinazolin-12(8H)-one (**41**). The two isomers are easily differentiated by their ir spectra, since **39** possesses a conjugated amide carbonyl (1620 cm^{-1}), whereas **41** possesses a nonconjugated amide carbonyl (1660 cm^{-1}). The ultraviolet maximum exhibited by **39** occurs at somewhat higher wavelengths (a bathochromic shift of 2–8 mμ) compared with the maximum exhibited by **41**.

A number of transformations of **39** were carried out to exploit the active methylene character of the allylic protons at position 1 (corresponding to C-17 by steroid numbering). This high methylene reactivity had been clearly exemplified by reactions exhibited by the model compounds previously discussed (**15** and **27**). Thus, the diaza steroid **39** gave a high yield of the chloral adduct **42** upon treatment with chloral in pyridine. When **39** was heated in a mixture of acetic anhydride and pyridine, a diacetyl derivative was obtained which exhibited a carbonyl band at 1760 cm^{-1}, characteristic of an imide. The diacetylation product must therefore



39, $X = H_2$
45, $X = NOH$
46, $X = CH_2$



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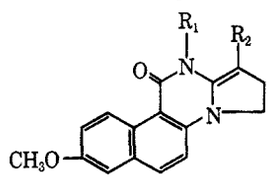
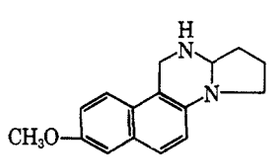
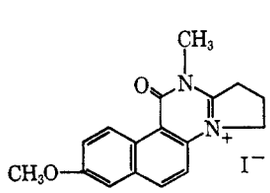


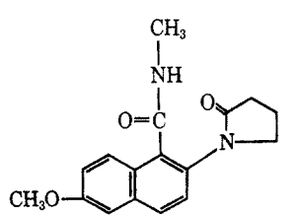
43, $R_1 = R_2 = COCH_3$
44, $R_1 = H$; $R_2 = COCH_3$



47



48



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be **43** in which both C and N acetylation had taken place. This structural assignment was confirmed by the nmr spectrum, which showed two different acetyl methyl groups. Mild alkaline hydrolysis of **43** selectively cleaved the N-acetyl grouping to give **44** in which the highest carbonyl stretching frequency was 1670

(13) F. H. S. Curd, C. G. Raison, and F. L. Rose, *J. Chem. Soc.*, 366 (1946).

(14) 2-Acetamidonaphthalene is known to monobrominate at position 1: W. Langenbeck and K. Hölscher, *Chem. Ber.*, **71**, 1465 (1938).

cm^{-1}, consonant with both intramolecular hydrogen bonding and α,β unsaturation (*cf.* compounds **19** and **20**). Only one broad hydrogen-bonded NH stretching band was observed for **44**.

In contrast to the unreactivity of the simple quinazolinone **15** with isoamyl nitrite, but consistent with the reactivity of **27**, the diaza steroid **39** reacted with the same reagent in the presence of sodium ethoxide to give the oxime **45**. Attempts to reduce the oxime either chemically or catalytically resulted in gums which resisted characterization. We have thus far been unable to prepare the parent carbonyl derivative.

Treatment of **39** with bis(dimethylamino)methane in acetic anhydride gave in excellent yield the *exo*-methylene derivative **46**. The same compound was obtained upon treatment of **39** with formaldehyde and dimethylamine hydrochloride under the usual Mannich reaction conditions, although in the latter case the yield was much inferior. The modified Mannich conditions [bis(dimethylamino)methane and acetic anhydride] may have some utility in the synthesis of olefins which usually result from pyrolysis of preformed Mannich bases.

Reduction of **39** with diborane in tetrahydrofuran gave in fair yield the crystalline, acid-soluble, parent diaza steroid, 8-methoxy-1,2,3,11,12,12a-hexahydrobenzo[*f*]pyrrolo[1,2-*a*]quinazoline (**47**). Attempts to form a picrate gave only gums, however, and attempted acetylation or methylation resulted in extensive decomposition. These difficulties may be associated with the ease with which this type of aminal undergoes ring opening in acid solution.[8]

Alkylation of **39** with methyl iodide gave a monoalkyl quaternary iodide which, like the monomethylation product of **15**, could possess one of four isomeric structures. Its nmr spectrum (see Experimental Section) confirmed N methylation; a strong band at 1700 cm^{-1} (ir spectrum) indicated retention of the carbonyl band. Its relatively high frequency for an amide carbonyl is presumably due to the same phenomenon responsible for the high frequency carbonyl band exhibited by compound **24**. The structure of the monoalkylation product of **39** thus appeared to be **48**, and this was confirmed by alkaline hydrolysis to N-[1-(N-methylcarbamoyl)-6-methoxy-2-naphthyl]pyrrolidone (**49**).

One interesting feature of the nmr spectra of the tetracyclic diaza steroids described above deserves special mention. All of the compounds bearing an amide carbonyl group in the position α to the naphthalene moiety exhibited a one-proton doublet at unusually low field (9.2 ppm, J = 9 cps). This low-field resonance signal, separated by more than 1 ppm downfield from the remainder of the aromatic protons, appeared to be due to the *peri* hydrogen of the naphthalene nucleus, which is strongly deshielded as a result of the magnetic anisotropy of the amide carbonyl group. That this effect is due to the anisotropy of the carbonyl function in a rigid planar system and is not a consequence of the electron-withdrawing ability of the carbonyl grouping is demonstrated by examination of the nmr spectrum of compound **49**, in which the lowest field aromatic proton doublet, presumably due to the *peri* hydrogen, appeared at 7.9 ppm. Furthermore, complete removal of the carbonyl grouping as in the reduction product **47** results in a shift of the *peri* hydrogen signal upfield so that it now lies under the multiplet of the remaining aromatic protons at about 7.2 ppm.

Experimental Section[15]

1-Cyano-2-naphthylamine (2)[5] was prepared from 2-naphthylamine-1-sulfonic acid by acetylation, bromination to 2-acetamido-1-bromonaphthalene,[16] reaction with cuprous cyanide in pyridine to give 2-acetamido-1-cyanonaphthalene, and finally alkaline hydrolysis of the acetamido grouping.

1-Cyano-2-succinamidonaphthalene (3).—A finely ground mixture of 33.6 g (0.2 mol) of 1-cyano-2-naphthylamine (**2**) and 20.0 g (0.2 mol) of succinic anhydride was fused by heating in an oil bath preheated to 140°. Heating was discontinued when the melt resolidified (10–15 min). The resulting solid was cooled, ground to a fine powder in a mortar, and stirred for 20 min in a suspension of 1 l. of 1 *N* sodium hydroxide solution. The resulting suspension was filtered to remove insoluble material, and the filtrate was acidified with dilute hydrochloric acid. The solid which precipitated was collected by filtration, washed with water, and dried *in vacuo* at 100° to give 45 g (84%) of **3**, mp 206–209°. The melting point was raised to 213–215° by recrystallization from absolute ethanol.

Anal. Calcd for $C_{15}H_{12}N_2O_3$: C, 67.15; H, 4.51; N, 10.44. Found: C, 66.94; H, 4.48; N, 10.23.

Ethyl β-(1,2-Dihydro-1-oxobenzo[*f*]quinazolin-3-yl)propionate (5).—Dry hydrogen chloride gas was passed through a suspension of 13.6 g of 1-cyano-2-succinamidonaphthalene (**3**) in 500 ml of *dry* ethanol for 4 hr. (Use of commercial absolute ethanol without predrying depressed the yield of the final product to 32%.) The system was protected from atmospheric moisture during this period with a calcium chloride tube. During the course of the reaction, the starting material slowly dissolved and a new crystalline solid separated. The reaction mixture was finally heated under reflux for 30 min, cooled to 0°, and filtered, and the collected solid was washed with dry ethanol to give 12.5 g (69%) of the hydrochloride salt of ethyl β-(1,2-dihydro-1-oxobenzo[*f*]quinazolin-3-yl)propionate, mp 265–270° dec. The free base was generated from the hydrochloride by boiling the latter for 15 min in water, followed by filtration and washing with water. The product was obtained in an over-all yield of 65% as colorless needles, mp 223–225°, by recrystallization from ethanol.

Anal. Calcd for $C_{17}H_{16}N_2O_3$: C, 68.90; H, 5.44; N, 9.45. Found: C, 68.83; H, 5.63; N, 9.71.

β-(1,2-Dihydro-1-oxobenzo[*f*]quinazolin-3-yl)propionic acid (6) was prepared from the ethyl ester (**5**) in 95% yield by saponification with 0.5 *N* sodium hydroxide solution under reflux for 0.5 hr. Acidification of the clear alkaline solution with dilute hydrochloric acid resulted in the separation of a solid which was collected by filtration, washed with ethanol, and dried to give 8.1 g of the free acid, mp 270–280° dec. The analytical sample, mp 273–277° dec, was prepared by recrystallization from a mixture of ethanol and dimethylformamide.

Anal. Calcd for $C_{15}H_{12}N_2O_3$: C, 67.15; H, 4.51; N, 10.44. Found: C, 66.87; H, 4.56; N, 10.48.

8,9-Dihydrobenzo[*f*]pyrrolo[2,1-*b*]quinazoline-10,12-dione (7).—A suspension of 1.0 g of β-(1,2-dihydro-1-oxobenzo[*f*]quinazolin-3-yl)propionic acid (**6**) in 60 ml of toluene was boiled until approximately 10 ml of the solvent had been removed (to effect removal of traces of moisture), and then 6 ml of acetic anhydride was added. The reaction mixture was then heated under reflux, with stirring, for 7 hr. A calcium chloride tube was employed to protect the mixture against atmospheric moisture. The hot homogeneous solution was treated with charcoal and filtered while hot, and the filtrate was cooled in an ice bath. The crystalline solid which separated was collected by filtration and washed with dry benzene to give 0.75 g (81%) of **7**, mp 214–216°. Recrystallization from a mixture of chloroform and heptane gave colorless crystals, mp 217–220°.

Anal. Calcd for $C_{15}H_{10}N_2O_2$: C, 71.99; H, 4.03; N, 11.20. Found: C, 71.82; H, 4.02; N, 11.13.

(15) All melting points are uncorrected. We are indebted for the microanalyses to the Robertson Microanalytical Laboratory, Florham Park, N. J., and to the Spang Microanalytical Laboratory, Ann Arbor, Mich. All nmr spectra were determined on a Varian A60-A spectrophotometer.

(16) M. C. Kloetzel, W. King, W. J. Wasserman, C. K. Warren, and P. A. Larseen, *J. Org. Chem.*, **26**, 607 (1961).

The imide structure of this product was confirmed by the presence of two carbonyl bands (1795 and 1695 cm^{-1}) in its ir spectrum, by its quantitative conversion upon boiling for 15 min in anhydrous ethanol into ethyl β-(1,2-dihydro-1-oxobenzo[*f*]quinazolin-3-yl)propionate (**5**), and by its quantitative conversion with hot water (10 sec) into the corresponding propionic acid (**6**).

7,7a,8,9,10,12-Hexahydrobenzo[*f*]pyrrolo[2,1-*b*]quinazoline (**9**).—A solution of 8.8 g of 8,9-dihydrobenzo[*f*]pyrrolo[2,1-*b*]-quinazoline-10,12-dione (**7**) in 360 ml of dry tetrahydrofuran was added dropwise over a period of 1 hr to 127 ml of a 1 *M* solution of diborane in tetrahydrofuran, maintained at 0°. Throughout the addition, the system was continually flushed with nitrogen. After addition was complete, the reaction mixture was heated under reflux for 2.5 hr, left overnight at room temperature, and then decomposed with 20 ml of 6 *N* hydrochloric acid. The organic solvent was removed by distillation, 200 ml of water was added, and the aqueous acidic solution was extracted with ethyl acetate. The aqueous layer was made alkaline with aqueous sodium hydroxide and extracted with ether. The dried ether extracts were concentrated under reduced pressure to give 1.1 g of a colorless crystalline solid; further concentration of the ether filtrates gave an additional 1.9 g. Recrystallization of this solid from ether gave a homogeneous (tlc) colorless solid, mp 104–107°.

Anal. Calcd for $C_{15}H_{16}N_2$: C, 80.32; H, 7.19; N, 12.49. Found: C, 79.84; H, 7.28; N, 12.39.

We were unable to convert this compound into derivatives because of its instability; it turned dark upon brief exposure to air and decomposed in contact with acetic anhydride, phenyl isocyanate, or phenyl isothiocyanate. Treatment of an acidic solution of this compound with sodium nitrite followed by addition of β-naphthol gave a positive diazo coupling test for a primary aromatic amine.

N-(1-Cyano-2-naphthyl)pyrrolidone (**12**).—A mixture of 2.0 g of 1-cyano-2-naphthylamine (**2**) and 1.3 g of butyrolactone was heated in a sealed steel bomb at 200° for 8 hr and then at 310° for an additional 9 hr. The cooled product was dissolved in 100 ml of ethanol and poured over 50 g of ice, and the resulting aqueous suspension was extracted with three 50-ml portions of ethyl acetate. The combined extracts were treated with charcoal, filtered, and dried over anhydrous magnesium sulfate. The ethyl acetate was removed by distillation under reduced pressure, and the oily residue was digested with 10 ml of hot ethanol. Cooling resulted in the separation of 1.4 g (50%) of **12**, mp 156–160°. Recrystallization from a mixture of ethyl acetate and heptane gave colorless needles: mp 157–159°; ir, 2200 (nitrile) and 1680 cm^{-1} (amide carbonyl).

Anal. Calcd for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86. Found: C, 76.20; H, 5.19; N, 11.69.

2,3-Dihydrobenzo[*f*]pyrrolo[1,2-*a*]quinazolin-11(1H)-one (**1**).—Dry hydrogen chloride gas was passed through a suspension of 1.0 g of N-(1-cyano-2-naphthyl)pyrrolidone (**12**) in 50 ml of dry ethanol at room temperature. After 2 hr the reaction mixture was heated under reflux for 30 min and cooled, and the precipitated hydrochloride was collected by filtration. The free base was liberated from its salt by dissolution in 50 ml of hot water and addition of 1 *N* sodium hydroxide solution to pH 8. The product, mp 300–305° dec, was obtained (60% yield) by filtration and recrystallization from hot dimethylformamide.

Anal. Calcd for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86. Found: C, 75.89; H, 5.24; N, 12.14.

β-(2-Methyl-1-oxo-1,2-dihydrobenzo[*f*]quinazolin-3-yl)propionic Acid (**13**).—To a stirred solution of 10.0 g of β-(1,2-dihydro-1-oxobenzo[*f*]quinazolin-3-yl)propionic acid (**6**) in 200 ml of 1 *N* sodium hydroxide solution was added dropwise 40 ml of dimethyl sulfate. The reaction mixture was stirred at room temperature for 3 hr with periodic additions of small amounts of sodium hydroxide solution to maintain basicity. Filtration then gave 6.0 g of **methyl β-(2-methyl-1-oxo-1,2-dihydrobenzo[*f*]quinazolin-3-yl)propionate**: mp 150–155°; ir, 1725 (ester carbonyl) and 1660 cm^{-1} (amide carbonyl). Its nmr spectrum showed methyl peaks at 3.48 (methyl ester) and 3.60 ppm (N-methyl).

Acidification of the filtrate above resulted in the separation of 2.1 g of the corresponding carboxylic acid, mp 217–220° dec. The analytical sample was prepared by recrystallization from ethanol and melted at 220–223° dec. The ir spectrum showed bands at 3100 (acidic proton), 1610 (acid carbonyl), and 1645 cm^{-1} (amide carbonyl); its nmr spectrum revealed the presence of only one methyl signal at 3.61 ppm (N-methyl). The methyl ester could be converted quantitatively into the acid by hydrolysis with 1 *N* sodium hydroxide solution in aqueous ethanol.

Anal. Calcd for $C_{16}H_{14}N_2O_3$: C, 68.07; H, 5.00; N, 9.92. Found: C, 68.05; H, 4.99; N, 9.94.

1-(N-Methylcarbamoyl)-2-aminonaphthalene.—A solution of 1.0 g of β-(2-methyl-1-oxo-1,2-dihydrobenzo[*f*]quinazolin-3-yl)-propionic acid (**13**) in 50 ml of 4 *N* sodium hydroxide solution was heated under reflux overnight under nitrogen. The basic solution was cooled and filtered, and the collected solid was washed with water to give 0.5 g (75%) of 1-(N-methylcarbamoyl)-2-aminonaphthalene, mp 227–229°. The product was recrystallized from ethyl acetate without change in the melting point.

Anal. Calcd for $C_{12}H_{12}N_2O$: C, 71.89; H, 6.04; N, 13.99. Found: C, 71.95; H, 6.21; N, 13.96.

1,2-Dimethylquinazolin-4(1H)-one (**15**).—To a stirred solution of 20.0 g of N-acetylanthranilonitrile (**16**) in 450 ml of 0.5 *N* sodium hydroxide was added, dropwise, 25 ml of dimethyl sulfate. After the solution became clear, an additional 20 ml of dimethyl sulfate was slowly added. The reaction mixture was then stirred until turbidity had disappeared; small portions of 0.5 *N* sodium hydroxide solution were added from time to time to maintain alkalinity. The reaction mixture was cooled, saturated with solid sodium carbonate, and extracted several times with ether. The combined ether extracts were dried over anhydrous magnesium sulfate and concentrated under reduced pressure, and the oily residue (19.0 g), which solidified at room temperature, was dissolved in 300 ml of dry ethanol. With stirring, a slow stream of dry hydrogen chloride gas was passed into this solution at room temperature for a period of 2 hr; slight warming of the reaction mixture was observed. It was then heated under reflux for 30 min, cooled in an ice bath, and filtered to give 15.8 g (60%) of 1,2-dimethylquinazolin-4(1H)-one hydrochloride, mp >320°.

The free base was obtained quantitatively from the above hydrochloride by addition of sodium acetate to a saturated aqueous solution, followed by cooling at 0° and filtration. The crude product was obtained as a hydrate which was dried overnight at 100° over phosphorus pentoxide *in vacuo* to give anhydrous **15**, mp 197–198° (lit.[9-11] mp 199°); the infrared spectrum of the product was identical with that reported.

1-Methyl-2-(3,3,3-trichloro-2-hydroxypropyl)quinazolin-4(1H)-one (**18**).—A solution of 1.05 g of 1,2-dimethylquinazolin-4-(1H)-one (**15**) and 0.93 g of chloral in 2.5 ml of anhydrous pyridine was heated on a steam bath for 45 min. The reaction mixture was cooled and poured over ice, and the solid which separated was collected by filtration, washed with water, and dried. Recrystallization from ethanol gave 1.35 g of **18**, mp 200–203° dec.

Anal. Calcd for $C_{12}H_{11}N_2O_2Cl_3$: C, 44.81; H, 3.37; N, 8.71. Found: C, 44.64; H, 3.55; N, 8.74.

The ir spectrum of **18** (Nujol) showed a broad OH band at 3100 and an amide carbonyl band at 1650 cm^{-1}. Its nmr spectrum in trifluoroacetic acid showed an N-methyl signal at 2.92, an AB quartet (J = 15.0 cps) centered at 3.62 (further split by the adjacent methine proton by 9.0 and 3.9 cps) exhibited by the methylene protons attached to C-2, and a single methine proton at 3.5 ppm, which appeared as a quadruplet with splitting of 3.9 and 9.0 cps.

2-Acetonylidene-2,3-dihydro-1-methylquinazolin-4(1H)-one (**19**).—A solution of 1.25 g of 1,2-dimethylquinazolin-4(1H)-one (**15**), 2.5 ml of pyridine, and 3 ml of acetic anhydride was heated on a steam bath for 3 hr. The reaction mixture was cooled and poured over ice, and the precipitated solid was collected by filtration, washed with water, and recrystallized from ethanol to yield 0.55 g (40%) of **19**, mp 263–266°. The product gave a positive ferric chloride test.

Anal. Calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.72; H, 5.64; N, 13.20.

2-Phenacylidene-2,3-dihydro-1-methylquinazolin-4(1H)-one (**20**).—To a solution of 1.74 g of 1,2-dimethylquinazolin-4(1H)-one (**15**) in 15 ml of anhydrous pyridine was added slowly 1.54 g of benzoyl chloride. The reaction mixture was heated on a steam bath for 15 min, cooled, and poured over ice, and the precipitated solid was collected by filtration and washed with water. The product (1.3 g, mp 246–249°, 47%) was purified by recrystallization from ethanol: mp 250–253°.

Anal. Calcd for $C_{17}H_{14}N_2O_2$: C, 73.36; H, 5.07; N, 10.07. Found: C, 73.63; H, 5.27; N, 9.78.

The product gave a positive ferric chloride test. It showed a single carbonyl band at 1685 cm^{-1} (Nujol), and its nmr spectrum in trifluoroacetic acid exhibited an N-methyl signal at 3.71, a complex aromatic multiplet, and a broad two-proton signal at 4.9 ppm which disappeared on heating the sample to 70° and reappeared on cooling.

3-[3,4-Dihydro-1-methyl-4-oxo-2(1H)-quinazolinylidene]-1,1,1,5,5,5-hexafluoro-2,4-pentanedione (21).—A mixture of 10.1 g of 1,2-dimethylquinazolin-4(1H)-one (**15**), 70 ml of dry tetrahydrofuran, and 50 ml of trifluoroacetic anhydride was stirred at room temperature for 3.5 hr and filtered, and the collected solid was washed with dry tetrahydrofuran. The crude product (19.9 g) was purified by recrystallization from a mixture of tetrahydrofuran and heptane: mp 250–252° dec.

Anal. Calcd for $C_{14}H_8N_2O_3F_6$: C, 45.90; H, 2.20; N, 7.65. Found: C, 45.94; H, 2.24; N, 7.91.

The product gave a negative ferric chloride test. It exhibited two carbonyl bands at 1725 and 1690 cm^{-1} (Nujol); its nmr spectrum in trifluoroacetic acid exhibited only an N-methyl signal and aromatic protons.

1-Methyl-2-ethoxalylmethylenequinazolin-4(1H)-one (22).—To a solution of 0.93 g of sodium ethoxide in 20 ml of dry ethanol was added 1.94 g of 1,2-dimethylquinazolin-4(1H)-one (**15**), followed by 1.60 g of diethyl oxalate. The reaction mixture was stirred overnight at room temperature, neutralized with acetic acid, and then diluted with 50 ml of water. The solid which separated was filtered, washed with water followed by ethanol, and dried to give 1.5 g (55%) of **22**, mp 270–273°. Recrystallization from hot dimethylformamide gave pale yellow needles, mp 277–280°.

Anal. Calcd for $C_{14}H_{14}N_2O_4$: C, 61.31; H, 5.15. N, 10.21. Found: C, 61.07; H, 5.15; N, 10.41.

The product gave a black coloration with ferric chloride solution. Its ir spectrum showed two carbonyl bands at 1725 (ester) and 1705 cm^{-1} (of double intensity and probably due to the hydrogen-bonded α,β-unsaturated ketone and the amide carbonyl combined). Its nmr spectrum in trifluoroacetic acid showed the expected N-methyl and ethyl signals and a broad, one-proton signal at 6.33 ppm which disappeared on heating to 70° and reappeared upon cooling to room temperature.

1,2,3-Trimethyl-4-oxo-1H-quinazolinium Iodide (24).—A solution of 1.0 g of 1,2-dimethylquinazolin-4(1H)-one (**15**) and 8 ml of methyl iodide in 20 ml of dried tetrahydrofuran was heated under reflux with stirring overnight in a nitrogen atmosphere. The reaction mixture was cooled and filtered to give 1.65 g (91%) of **24**, mp 253–255° dec, which was purified by recrystallization from a mixture of dimethyl sulfoxide–ethanol–ether: mp 255–257° dec.

Anal. Calcd for $C_{11}H_{13}N_2OI$: C, 41.79; H, 4.11; N, 8.86. Found: C, 41.80; H, 4.09; N, 8.65.

The product exhibited a single carbonyl band at 1705 cm^{-1} (Nujol); its nmr spectrum in trifluoroacetic acid showed three distinct methyl signals at 2.79, 3.55, and 3.84 ppm.

N-(o-Cyanophenyl)-4-chlorobutyramide (25).—4-Chlorobutyryl chloride (14.1 g, 0.11 mol) was added dropwise to a cooled, stirred solution of anthranilonitrile (11.9 g, 0.10 mol) in 50 ml of dry pyridine. The solution was left overnight at room temperature and then poured into *ca.* 250 ml of water and the solution was acidified with dilute hydrochloric acid. The mixture was then extracted with three 75-ml portions of chloroform, the combined extracts were dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure to give 22.1 g (99%) of a light tan solid, mp 88–91°. The analytical sample, mp 93–95°, was prepared by repeated crystallization from carbon tetrachloride–petroleum ether (bp 40–60°).

Anal. Calcd for $C_{11}H_{11}N_2OCl$: C, 59.33; H, 4.98; N, 12.58. Found: C, 59.09; H, 5.10; N, 12.81.

N-(o-Cyanophenyl)pyrrolidin-2-one (26).—A solution of sodium hydroxide (6.0 g, 0.15 mol) in 20 ml of water was added to a solution of 13.5 g (0.061 mol) of N-(*o*-cyanophenyl)-4-chlorobutyramide (**25**) in 125 ml of methanol. The solution was allowed to stand at room temperature for 2.5 hr, during which time a precipitate gradually separated. The mixture was then added to 300 ml of water and extracted with 3 100-ml portions of chloroform. The combined extracts were washed with 200 ml of 1 *N* hydrochloric acid (the color of the chloroform layer changed from orange to yellow during this washing process), and the organic layer was dried over anhydrous magnesium sulfate and evaporated to dryness to give 6.9 g (61%) of **26**, mp 72–81°. The analytical sample, mp 93–95°, was prepared by repeated crystallization from ethyl acetate–petroleum ether (bp 40–60°).

Anal. Calcd for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.05. Found: C, 71.03; H, 5.28; N, 14.93

2,3-Dihydropyrrolo[1,2-a]quinazolin-9(1H)-one (27).—Dry hydrogen chloride gas was bubbled through a solution of 2.0 g (0.011 mol) of N-(*o*-cyanophenyl)pyrrolidin-2-one (**26**) in 50 ml of absolute ethanol for 3 hr. The solution became warm and a white solid separated. The reaction mixture was cooled and filtered, and the collected solid was dissolved in 50 ml of water; this solution was neutralized with sodium acetate and then extracted with three 75-ml portions of chloroform. The combined extracts were dried over anhydrous sodium sulfate and the solvent was evaporated to give 1.86 g (93%) of **27**, mp 216–219°. The analytical sample, mp 217–219°, was prepared in the form of fawn-colored needles by recrystallization from chloroform–petroleum ether (bp 40–60°).

Anal. Calcd for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.05. Found: C, 71.10; H, 5.69; N, 15.01.

The nmr spectrum (deuteriochloroform) showed a quintuplet at 2.38 (two C_2 protons), a triplet at 3.12 (two C_1 protons), a triplet at 4.23 (two C_3 protons), a multiplet at 7.00–7.82 due to the aromatic protons at C_5, C_6, and C_7, and a separate, downfield doublet at 8.15 ppm due to the deshielded C_8 proton.

2,3-Dihydropyrrolo[1,2-a]quinazoline-1,9-dione 1-Oxime (28).—To a solution of 1.86 g of 2,3-dihydropyrrolo[1,2-*a*]quinazolin-9(1H)-one (**27**) in 50 ml of ethanol containing 1.15 g of sodium was added 2.8 g of isoamyl nitrite, and the mixture was allowed to stir under nitrogen overnight. It was then neutralized with acetic acid and diluted with water, and the solid which had separated was collected by filtration, washed well with water followed by ethanol, and dried to yield 1.6 g (74%) of **28**. The analytical sample, mp >340° with charring, was prepared by recrystallization from hot dimethylformamide.

Anal. Calcd for $C_{11}H_9N_3O_2$: C, 61.39; H, 4.22; N, 19.53. Found: C, 60.92; H, 4.37; N, 19.46.

The nmr spectrum (trifluoroacetic acid) showed a two-proton triplet at 4.48 (C_3-methylene) and a two-proton triplet at 3.06 ppm (C_2-methylene).

2,3-Dihydro-1-methylenepyrrolo[1,2-a]quinazolin-9(1H)-one (29).—To a suspension of 0.81 g of 2,3-dihydropyrrolo[1,2-*a*]-quinazolin-9(1H)-one (**27**) in 5 ml of bis(dimethylamino)methane was added 5 ml of acetic anhydride. An exothermic reaction ensued. The reaction mixture was then allowed to stand overnight at 0° and filtered, and the collected solid was washed with ether to give 0.68 g (79%) of **29**, mp 207–209°.

Anal. Calcd for $C_{12}H_{10}N_2O$: C, 72.71; H, 5.09; N, 14.13. Found: C, 72.89; H, 5.18; N, 13.86.

Characteristic features of the nmr spectrum (deuteriochloroform) were a four-proton aromatic multiplet at 7.05–8.20, two closely spaced triplets (one proton each) at 6.40 and 5.51 (exomethylene group), a two-proton triplet at 4.17 (J = 6 cps; C_3-methylene group), and a two-proton broad triplet at 3.08 ppm (C_2-methylene group).

2-Acetamido-1-bromo-6-methoxynaphthalene (32).—To a stirred, cooled solution of 23.5 g (0.014 mol) of 6-methoxy-2-naphthylamine (**30**) in 100 ml of glacial acetic acid was added slowly, and over a period of 30 min, a solution of 22 g (0.14 mol) of bromine in 50 ml of glacial acetic acid. Immediate precipitation occurred when the bromine was added. After addition was complete, the precipitated solid was collected by filtration and washed well with acetic acid followed by ether; the crude product (46 g) was acetylated at room temperature with a mixture of 50 ml of anhydrous pyridine and 100 ml of acetic anhydride. After standing overnight at room temperature, the acetylation mixture deposited a crystalline solid which was collected by filtration and washed well with ethanol followed by ether to yield 27 g, mp 165–173°. This crude product, which was a mixture of mono- and dibromo products, was separated by leaching with 300 ml of hot ethanol.

Concentration of the ethanol extracts yielded 17.7 g (47%) of 2-acetamido-1-bromo-6-methoxynaphthalene, mp 177–182°. Recrystallization from ethanol raised the melting point to 183–186°.[17]

(17) The low carbon value was the result of slight contamination by the dibromo derivative, which could not be removed by further fractional crystallization. However, subsequent products prepared from **32** gave satisfactory analyses.

Anal. Calcd for $C_{13}H_{12}NO_2Br$: C, 53.08; H, 4.11; N, 4.76. Found: C, 51.68; H, 4.01; N, 4.52.

The ethanol-insoluble material, probably 1,5-dibromo-6-methoxy-2-acetamidonaphthalene (**31**) (4.6 g, mp 225–240°), was recrystallized from dimethylformamide; the analytical sample melted at 241–244°.

Anal. Calcd for $C_{13}H_{11}NO_2Br_2$: C, 41.85; H, 2.97; N, 3.76. Found: C, 41.92; N, 2.98; N, 3.88.

3-Methyl-8-methoxybenzo[*h*]quinazolin-1(2H)-one (34).—A mixture of 32 g of 2-acetamido-1-bromo-6-methoxynaphthalene (**32**), 13 g of cuprous cyanide (freshly prepared), and 20 ml of anhydrous pyridine in a 100-ml flask fitted with a reflux condenser was heated in an oil bath at 200° for 3 hr. The hot black reaction mixture was poured with vigorous stirring into 2 l. of 5 *N* aqueous ammonium hydroxide. The resulting suspension was stirred for 2.5 hr and the brown solid was collected, washed with dilute ammonium hydroxide and water, and dried. Recrystallization of the crude product from 50% aqueous ethanol gave **2-acetamido-1-cyano-6-methoxynaphthalene** as colorless crystals, mp 198–200°, in 57% yield.

Dry hydrogen chloride gas was bubbled through a suspension of 1.4 g of crude 2-acetamido-1-cyano-6-methoxynaphthalene, prepared as described above, in 60 ml of dry ethanol. After 1.5 hr the gas flow was discontinued, the reaction mixture was heated under reflux for 30 min and cooled, and the separated solid was collected by filtration and washed with cold anhydrous ethanol. The resulting product was suspended in water and the pH adjusted to 9 with dilute ammonium hydroxide. Filtration then gave 1.2 g (86%) of **34** which upon recrystallization from dimethylformamide melted at 340–344° dec.

Anal. Calcd for $C_{14}H_{12}N_2O_2$: C, 69.99; H, 5.18; N, 11.66. Found: C, 70.26; H, 5.18; N, 11.65.

The nmr spectrum of the product in trifluoroacetic acid was completely in accord with the assigned structure (**34**); the only feature worthy of note is the downfield shift of the aromatic protons at C_5 and C_{10}, characteristics of such cyclic systems.

1-Cyano-6-methoxy-2-naphthylamine (35).—A suspension of 10.0 g of 2-acetamido-1-cyano-6-methoxynaphthalene (obtained as described above under the preparation of **34**) in 140 ml of 1 *N* sodium hydroxide solution was heated under reflux with vigorous stirring for 30 min; extensive foaming occurred. The resulting suspension was cooled and filtered, and the collected solid was washed with dilute sodium hydroxide solution followed by water to give 7.8 g (94%) of **35**, mp 203–207°; the melting point was raised to 205–207° by recrystallization from ethyl acetate.

Anal. Calcd for $C_{12}H_{10}N_2O$: C, 72.71; H, 5.09; N, 14.13. Found: C, 72.54; H, 5.02; N, 13.97.

8,9-Dihydro-3-methoxybenzo[*f*]pyrrolo[2,1-*b*]quinazoline-10,12-dione (36) was prepared from 1-cyano-6-methoxy-2-naphthylamine (**35**) by fusion with succinic anhydride, cyclization to the quinazolinone with dry hydrogen chloride in anhydrous ethanol, hydrolysis, and subsequent cyclodehydration with acetic anhydride in refluxing toluene, in a manner patterned exactly after the preparation of 8,9-dihydrobenzo[*f*]pyrrolo-[2,1-*b*]quinazoline-10,12-dione (**7**) described above. The product was obtained in 30% over-all yield in the form of colorless needles, mp 239–241° dec upon recrystallization from chloroform.

Anal. Calcd for $C_{16}H_{12}N_2O_3$: C, 68.56; H, 4.32; N, 10.00. Found: C, 68.22; H, 4.29; N, 9.76.

4-Chloro-N-(1-cyano-6-methoxy-2-naphthyl)butyramide (37).—To a suspension of 5.4 g of 1-cyano-6-methoxy-2-naphthylamine (**35**) in 50 ml of anhydrous pyridine was added slowly and with stirring 7.5 g of freshly distilled 4-chlorobutyryl chloride. The reaction mixture was allowed to stand at room temperature overnight and poured over ice, and the solid which separated was collected by filtration, washed with water, and recrystallized from ethanol. The yield of **37** was 5.1 g (61%), mp 158–165°. Recrystallization from ethanol then gave white needles, mp 168–170°.

Anal. Calcd for $C_{16}H_{15}N_2O_2Cl$: C, 63.3; H, 4.98; N, 9.25. Found: C, 63.3; H, 5.08; N, 9.14.

N-(1-Cyano-6-methoxy-2-naphthyl)pyrrolidone (38).—To a suspension of 2.7 g of 4-chloro-N-(1-cyano-6-methoxy-2-naphthyl)-butyramide (**37**) in 90 ml of anhydrous ethanol was added 3.6 g of sodium methoxide. The mixture became homogeneous and turned pale yellow, and after a few minutes a colorless solid started to separate. The mixture was left overnight at room temperature, neutralized with acetic acid, diluted with 150 ml of water, and filtered. The collected solid was washed well with water and recrystallized from ethanol (charcoal) to give 1.8 g (76%) of **38** as shiny plates, mp 165–167°. Recrystallization from ethanol sharpened the melting point to 166–167°.

Anal. Calcd for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52. Found: C, 72.10; H, 5.07; N, 10.56.

2,3-Dihydro-8-methoxybenzo[*f*]pyrrolo[1,2-*a*]quinazolin-11-(1H)-one (39).—Dry hydrogen chloride gas was passed for a period of 2.5 hr at room temperature through a suspension of 1.8 g of N-(1-cyano-6-methoxy-2-naphthyl)pyrrolidone (**38**) in 120 ml of anhydrous ethanol. The reaction mixture was finally heated under reflux for 30 min and cooled, and the precipitated solid was collected and washed well with ethanol. The yield of the hydrochloride of **39** was 1.88 g (92%). This material was dissolved in 100 ml of hot water; 1.8 g of sodium acetate was added; the crystalline colorless product which separated on cooling was filtered, washed with water, and recrystallized from a mixture of ethanol and dimethylformamide to give colorless crystals, mp 260–270° dec.

Anal. Calcd for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52. Found: C, 71.96; H, 5.39; N, 10.28.

3-(3-Chloropropyl)-8-methoxybenzo[*h*]quinazolin-1(2H)-one (40).—Dry hydrogen chloride gas was passed for a period of 2.5 hr with stirring, and at room temperature, through a suspension of 2.0 g of 4-chloro-N-(1-cyano-6-methoxy-2-naphthyl)-butyramide (**37**) in 130 ml of anhydrous ethanol. The resulting suspension was cooled to 0° and filtered, and the collected solid was washed with ethanol to give 1.85 g (82%) of the hydrochloride of **40**. This material was suspended in 80 ml of water and heated on a steam bath for 10 min. The resulting suspension was cooled and filtered, and the filter cake was washed well with water followed by ethanol. Recrystallization from anhydrous tetrahydrofuran gave colorless crystals, mp 285–290° dec.

Anal. Calcd for $C_{16}H_{15}N_2O_2Cl$: C, 63.50; H, 4.99; N, 9.25. Found: C, 63.21; H, 5.20; N, 8.95.

9,10-Dihydro-3-methoxybenzo[*f*]pyrrolo[2,1-*b*]quinazolin-12-(8H)-one (41).—A suspension of 1.2 g of 3-(3-chloropropyl)-8-methoxybenzo[*h*]quinazolin-1(2H)-one (**40**), 1.4 g of sodium methoxide, and 30 ml of anhydrous ethanol was stirred at room temperature for 5 hr. The reaction mixture was then neutralized with acetic acid, 50 g of ice was added, and the precipitated solid was collected by filtration and washed with water to yield 0.95 g of a solid which proved (tlc) to be a mixture of two components. The mixture was suspended in 40 ml of 1 *N* hydrochloric acid, heated on a steam bath for 10 min, and filtered while hot, and the filter cake was washed with cold water. The solid so obtained weighed 0.63 g (52%), mp 300° dec, and proved to be the hydrochloride of **41**. The free base was obtained by suspending the above salt in 15 ml of hot water and adding 0.6 g of sodium acetate. The suspension was cooled to 0° and filtered, and the collected solid was recrystallized from ethanol to give colorless crystals, mp 193–195°.

Anal. Calcd for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52. Found: C, 72.31; H, 5.47; N, 10.52.

The acidic filtrate above was adjusted to alkalinity by the addition of 6 *N* sodium hydroxide solution and the precipitated solid collected by filtration and washed with water to give 0.3 g (29%) of the isomeric tetracyclic diaza steroid, 2,3-dihydro-8-methoxybenzo[*f*]pyrrolo[1,2-*a*]quinazolin-11(1H)-one (**39**). One recrystallization from ethanol gave colorless crystals, mp 267–270° dec, identical with a sample of **39** prepared as described above by acid-catalyzed cyclization of N-(1-cyano-6-methoxy-2-naphthyl)pyrrolidone.

2,12-Dihydro-8-methoxy-1-(2,2,2-trichloro-1-hydroxyethyl)-benzo[*f*]pyrrolo[1,2-*a*]quinazolin-11(1H)-one (42).—A suspension of 1.3 g of the hydrochloride of 2,3-dihydro-8-methoxybenzo-[*f*]pyrrolo[1,2-*a*]quinazolin-11(1H)-one (**39**) and 1.0 g of chloral in 12 ml of anhydrous pyridine was heated on a steam bath for 45 min. The homogeneous solution was poured over ice, and the precipitated solid was collected by filtration and then washed well with water to give 1.78 g (100%) of **42**. The analytical sample, mp 350° with charring, was prepared by recrystallization from aqueous dimethylformamide. The methine proton of the $CH(OH)CCl_3$ substituent was discernible in the nmr spectrum (trifluoroacetic acid) as a doublet ($J \sim 3$ cps) at 4.7 ppm, indicating a tautomeric structure for **42** analogous to that established for the chloral adduct **18**.

Anal. Calcd for $C_{18}H_{15}N_2O_3Cl_3$: C, 52.26; H, 3.65; N, 6.77. Found: C, 52.48; H, 3.82; N, 7.02.

1,12-Diacetyl-2,12-dihydro-8-methoxybenzo[*f*]pyrrolo[1,2-*a*]-quinazolin-11(3H)-one (43).—A suspension of 2.1 g of 2,3-

dihydro-8-methoxybenzo[*f*]pyrrolo[1,2-*a*]quinazolin-11(1H)-one (**39**) in 21 ml of anhydrous pyridine and 21 ml of acetic anhydride was heated under reflux for 1 hr, whereupon it became homogeneous. The reaction mixture was cooled to 0° and filtered, and the collected solid was washed by water followed by ethanol and recrystallized from dimethylformamide to give 1.45 g (60%) of pale yellow needles, mp 268–270° dec.

Anal. Calcd for $C_{20}H_{18}N_2O_4$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.77; H, 5.34; N, 8.22.

The infrared spectrum of this product showed carbonyl bands at 1700 (α,β-unsaturated carbonyl at C_1), 1760 (the N_{12}-acetyl imide carbonyl), and 1635 cm^{-1} (C_{11}-amide). Its nmr spectrum in trifluoroacetic acid showed five aromatic protons, a two-proton triplet (J = 7 cps) at 4.40 attributed to the methylene group at C_3, a two-proton triplet (J = 7 cps) at 2.90 attributed to the methylene group at C_2, a sharp methoxyl three-proton singlet at 3.65, and two acetyl methyl signals at 2.26 and 1.98 ppm.

1-Acetyl-2,12-dihydro-8-methoxybenzo[*f*]pyrrolo[1,2-*a*]quinazolin-11(3H)-one (**44**).—A suspension of 4.52 g of 1,12-diacetyl-2,12-dihydro-8-methoxybenzo[*f*]pyrrolo[1,2-*a*]quinazolin-11(3H)-one (**43**), 4.50 g of sodium methoxide, and 300 ml of anhydrous ethanol was stirred under nitrogen at room temperature for 4.5 hr. The reaction mixture was then neutralized with acetic acid, cooled, and filtered to give 3.9 g (98%) of **44**. Recrystallization from dimethylformamide gave yellow needles, mp 272–275°.

Anal. Calcd for $C_{18}H_{16}N_2O_3$: C, 70.11; H, 5.23; H, 9.09. Found: C, 70.32; H, 5.25; N, 9.26.

The ir spectrum of the product showed the presence of two carbonyl bands at 1670 and 1640 cm^{-1}. Its nmr spectrum in trifluoroacetic acid showed five aromatic protons, a two-proton multiplet at 4.27 attributed to the C_3-methylene group, a two-proton multiplet at 2.82 attributed to the C_2-methylene, a methoxy signal at 3.6, and a single acetyl methyl signal at 1.97 ppm.

2,3-Dihydro-8-methoxybenzo[*f*]pyrrolo[1,2-*a*]quinazoline-1,11-dione 1-Oxime (**45**).—To a stirred suspension, under nitrogen, of 2.66 g of 2,3-dihydro-8-methoxybenzo[*f*]pyrrolo[1,2-*a*]-quinazolin-11(1H)-one (**39**) in 50 ml of anhydrous ethanol containing 1.15 g of sodium was added 2.8 g of isoamyl nitrite. The reaction mixture was heated at 60° for 30 min and then stirred at room temperature for 22 hr. It was then cooled and diluted with 30 ml of ethanol and the mixture was filtered to remove insoluble material. The filtrate was acidified with acetic acid to give a pale yellow crystalline solid which was collected by filtration and washed with ethanol to yield 2.0 g of **45**, mp 300° dec. The infrared spectrum of this material showed a broad band centered at 3050 cm^{-1} attributed to the acidic oxime hydrogen. The product was insoluble in organic or aqueous solvents and could not be satisfactorily recrystallized for analysis.

2,3-Dihydro-8-methoxy-1-methylenebenzo[*f*]pyrrolo[1,2-*a*]-quinazolin-11(1H)-one (**46**).—To a suspension of 0.83 g of 2,3-dihydro-8-methoxybenzo[*f*]pyrrolo[1,2-*a*]quinazolin-11(1H)-one (**39**) in 12 ml of bis(dimethylamino)methane was added 12 ml of acetic anhydride. A vigorous exothermic reaction ensued, the reaction mixture became homogeneous, and after several minutes a crystalline solid separated. The reaction mixture was cooled and filtered to give 0.65 g (75%) of a colorless crystalline solid, mp 265–270° dec. The analytical sample was prepared by recrystallization from dimethylformamide. The same compound could be obtained in lower yield from **39** under the normal Mannich reaction conditions utilizing dimethylamine hydrochloride and formaldehyde.

Anal. Calcd for $C_{17}H_{14}N_2O_2$: C, 73.36; H, 5.07; N, 10.07. Found: C, 73.38; H, 5.01; N, 10.14.

The infrared spectrum of this compound showed two bands at 1635 and 1620 cm^{-1} (C_{11}-carbonyl and C=N). Its nmr spectrum in trifluoroacetic acid showed the presence of five aromatic protons, a two-proton triplet at 4.50 ppm attributed to the C_3-methylene group, a broad two-proton triplet at 3.00 ppm attributed to the C_2-methylene group, and a methoxyl signal at 3.62 ppm. The exocyclic methylene hydrogens appeared as a pair of multiplets at 6.40 and 5.92 ppm.

8-Methoxy-1,2,3,11,12,12a-hexahydrobenzo[*f*]pyrrolo[1,2-*a*]-quinazoline (**47**).—A suspension of 2.5 g of 2,3-dihydro-8-methoxybenzo[*f*]pyrrolo[1,2-*a*]quinazolin-11(1H)-one (**39**) in 80 ml of anhydrous tetrahydrofuran was cooled to 0° in an ice bath and 35 ml of a 1 *M* diborane solution in tetrahydrofuran was added dropwise over a period of 30 min. During this time the system was stirred and kept under nitrogen. After addition was complete, the reaction mixture was heated under reflux for 6 hr, left at room temperature overnight, and then decomposed by the addition of 6 ml of 6 *N* hydrochloric acid solution. The tetrahydrofuran was removed by distillation and 100 ml of water was added to the residue. The insoluble solid which separated was collected by filtration and washed with water to yield 1.27 g of the hydrochloric acid salt of the desired reduction product **47**. The filtrate was adjusted to neutrality with aqueous sodium hydroxide and the resulting turbid solution was extracted with ether. The combined extracts were dried over anhydrous magnesium sulfate and concentrated to give 0.2 g of a colorless crystalline solid, mp 148–151°, which upon recrystallization from tetrahydrofuran and heptane melted at 150–152°. An additional quantity of **47** was obtained by treatment of the hydrochloride salt, obtained as described above, with sodium acetate in hot water.

Anal. Calcd for $C_{16}H_{18}N_2O$: C, 75.56; H, 7.13; N, 11.02. Found: C, 74.82; H, 7.09; N, 10.75.

The nmr spectrum of this compound in deuteriochloroform showed the following features: an aromatic multiplet at 7.2 (five aromatic protons); a peak at 4.17 (total intensity three protons) consisting of the two C_{11} protons overlapping with the C_{12a}-proton multiplet; a three-proton singlet at 3.8 (methoxyl); multiplets at 3.25 (two protons, C_3) and 1.4–2.2 (four protons, C_1 and C_2); and a singlet at 1.1 ppm due to the proton on N_{12}.

2,3,11,12-Tetrahydro-8-methoxy-12-methyl-11-oxo-1H-benzo-[*f*]pyrrolo[1,2-*a*]-quinazolin-4-ium Iodide (**48**).—A solution of 2.0 g of 2,3-dihydro-8-methoxybenzo[*f*]pyrrolo[1,2-*a*]quinazolin-11(1H)-one (**39**) in 50 ml of tetrahydrofuran containing 10 ml of methyl iodide was heated under reflux with stirring overnight under nitrogen. The reaction mixture was cooled and the precipitated solid was collected by filtration and washed with ether. Recrystallization from dimethyl sulfoxide gave 2.9 g (92%) of **48**, mp 290–295° dec.

Anal. Calcd for $C_{17}H_{17}N_2O_2I$: C, 50.1; H, 4.20; N, 6.85. Found: C, 49.6; H, 4.65; H, 6.33.

The amide carbonyl band appeared at 1700 cm^{-1}; the nmr spectrum in trifluoroacetic acid showed a methoxyl at 3.42 and an N-methyl signal at 4.00 ppm.

N-[1-(N-Methylcarbamoyl)-6-methoxy-2-naphthyl]pyrrolidone (**49**).—A suspension of 0.7 g of 2,3,11,12-tetrahydro-8-methoxy-12-methyl-11-oxo-1H-benzo[*f*]pyrrolo[1,2-*a*]quinazolin-4-ium iodide (**48**) in 40 ml of 1 *N* sodium hydroxide solution was stirred at room temperature. The solid slowly dissolved and shortly a white crystalline solid started to separate. After 1 hr, this was collected by filtration, washed with water, dried, and recrystallized from acetone–heptane to give 0.4 g (75%) of **49**, mp 161–163°.

Anal. Calcd for $C_{17}H_{18}N_2O_3$: C, 68.44; H, 6.08; N, 9.39. Found: C, 68.39; H, 6.04; N, 9.29.

The $-NHCH_3$ grouping was confirmed by the nmr spectrum of **49**, which exhibited a split N-CH_3 signal (J = 4 cps) at 3.0 ppm.

Registry No.—**1**, 16201-72-2; **3**, 16201-73-3; **5**, 16201-74-4; **5** hydrochloride, 16201-75-5; **6**, 16201-76-6; **7**, 16240-71-4; **9**, 16201-77-7; **12**, 16201-78-8; **13**, 16201-88-0; **14**, 16201-79-9; **15**, 7471-65-0; **15** hydrochloride, 16201-81-3; **18**, 16240-72-5; **19**, 16201-82-4; **20**, 16201-83-5; **21**, 16201-84-6; **22**, 16201-85-7; **24c**, 16201-86-8; **25**, 16201-87-9; **26**, 16240-73-6; **27**, 16198-97-3; **28**, 16198-98-4; **29**, 16240-75-8; **31**, 16198-80-4; **32**, 16198-81-5; **34**, 16198-82-6; **35**, 16198-83-7; **36**, 16198-84-8; **37**, 16198-85-9; **38**, 16198-86-0; **39**, 16198-87-1; **40**, 16198-88-2; **41**, 16198-89-3; **41** hydrochloride, 16198-90-6; **42**, 16198-91-7; **43**, 16198-92-8; **44**, 16198-93-9; **45**, 16198-94-0; **46**, 16240-74-7; **47**, 16198-95-1; **48**, 16198-96-2; **49**, 16198-99-5; 1-(N-methylcarbamoyl)-2-aminonaphthalene, 16199-00-1; 2-acetamido-1-cyanomethoxynaphthalene, 16199-01-2.