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HETEROCYCLIC SYNTHESES FROM *o*-AMINONITRILES—XXVIII[1]

SYNTHESIS OF SOME BENZO(*f*)- AND BENZO(*h*)QUINAZOLINES[2]

E. C. TAYLOR, A. MCKILLOP, Y. SHVO and G. H. HAWKS
Princeton University, Princeton, New Jersey 08540

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Abstract—Starting with 1-cyano-6-methoxynaphthalene, approaches have been made to the synthesis of derivatives of the benzo(*f*)quinazoline ring system as analogs of the folic acid antagonist and antimalarial agent pyrimethamine, in which the 5-aryl grouping in the latter compound has been tied back to the pyrimidine ring by an ethylene bridge. A series of related 5,6-dihydrobenzo(*h*)quinazolines (incorporating an ethano bridge) has been prepared from 6-methoxy-1-tetralone *via* 2-hydroxymethylene-6-methoxy-1-tetralone, 2-methoxymethylene-6-methoxy-1-tetralone, and 2-dimethylaminomethylene-6-methoxy-1-tetralone. A summary is given of unsuccessful attempts to prepare 1-amino-2-cyano-6-methoxy-3,4-dihydronaphthalene.

THE interesting pharmacological spectrum of 2,4-diamino-5-(*p*-chlorophenyl)-6-ethylpyrimidine (pyrimethamine, "Daraprim") (I)[3a–d] has stimulated numerous recent studies on the preparation of related pyrimidine derivatives in a search for structural requirements for optimal antifolic acid and antimalarial activity. In a study of 2,2-dialkyl-4,6-diamino-1-aryl-1,2-dihydro-*s*-triazines,[4] it was suggested that structures in which both the triazine ring and the aryl grouping were as close to coplanarity as possible favored optimal antifolic acid activity. It seemed to us that compounds related to pyrimethamine in which the 5-aryl grouping was tied back through a suitable bridge to the pyrimidine ring might satisfy this requirement for coplanarity and thus lead to new systems with potentially interesting pharmacological activities. Incorporation of an ethylene bridge in the 5-arylpyrimidine system of I leads to the benzo(*f*)quinazoline system II. In view of recent reports[5] which describe the preparation of 1,3-diaminobenzo(*f*)quinazoline as a potential enzyme inhibitor, based upon the same rationale (as well as the synthesis of the parent ring system II),[5] we describe in this paper only the preparation of a selected number of derivatives of II, which have employed synthetic methods not discussed.[5] We also describe the preparation of a number of derivatives of the isomeric benzo(*h*)quinazoline ring system (III) in which

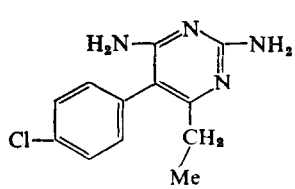
[1] For the previous paper in this series, see E. C. Taylor, A. McKillop and R. N. Warrener, *Tetrahedron* **23**, 891 (1967).

[2] This work was supported by a generous grant to Princeton University from the Smith Kline and French Laboratories, Philadelphia, Penna.

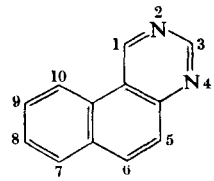
[3a] P. B. Russell and G. H. Hitchings, *J. Am. Chem. Soc.* **73**, 3763 (1951); [b] E. A. Falco, L. G. Goodwin, G. H. Hitchings, I. Rollo and P. B. Russell, *Brit. J. Pharmacol.* **6**, 185 (1951); [c] G. H. Hitchings, E. A. Falco, H. VanderWerff, P. B. Russell and G. B. Elion, *J. Biol. Chem.* **199**, 43 (1952); [d] P. B. Russell in *Medicinal Chemistry* (Edited by A. Burger; 2nd Edition) pp. 814–850. Interscience, New York (1960).

[4] E. J. Modest, S. Farber and G. E. Foley, *Proc. Am. Assoc. Cancer Res.* **1**, 33 (1954).

[5a] A. Rosowsky, N. Papathanasopoulos, M. E. Nadel, S. K. Sengupta and E. J. Modest, *Abstracts of Papers*, 151*st Meeting, ACS* No. 1. Sect. I. Pittsburgh, Pa. March 28 (1966); [b] A. Rosowsky and E. J. Modest, *J. Org. Chem.* **31**, 2607 (1966); [c] E. J. Modest, A. Rosowsky, S. Farber and G. E. Foley, *Abstracts of Papers*, 9*th International Cancer Congress*. Tokyo, Japan, in press.



I



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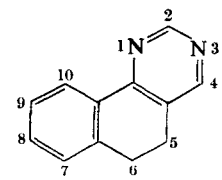


III

the bridge joining the aryl substituent to the pyrimidine ring is an ethano rather than an ethylene grouping.[6] Considerable attention is given to a discussion of the chemistry associated with attempts to prepare intermediates of interest in the latter program.

During the course of our recent studies on the total synthesis of azasteroids,[7] we had occasion to prepare substantial quantities of 1-cyano-6-methoxy-2-naphthylamine (IV). The versatility of *o*-aminonitriles for the synthesis of fused pyrimidines has been the subject of numerous publications;[8] the latter intermediate thus appeared to be ideally suited for the preparation of the desired pyrimethamine analogs in the benzo(*f*)quinazoline series.[9] Treatment of IV with phenylisocyanate in boiling xylene yielded 1-phenyl-3-(6-methoxy-1-cyano-2-naphthyl)urea (V) which was cyclized with sodium methoxide in ethanol to 2-phenyl-1-imino-1,2-dihydro-8-methoxybenzo-(*f*)quinazoline-3(4*H*)-one (VI).[10] The structure of this intramolecular cyclization product was readily established by acid hydrolysis to 2-phenyl-8-methoxy-benzo(*f*)-quinazoline-1,3(2*H*,4*H*)-dione (VII). Rearrangement of VI to the isomeric 1-anilino derivative VIII was effected by heating in nitrobenzene solution. The structure of the rearranged product was established by acid hydrolysis to 8-methoxybenzo(*f*)quinazoline-1,3(2*H*,4*H*)-dione (IX). This method provides a satisfactory alternative to the procedure devised[5] for the preparation of the 8-desmethoxy derivative.

Condensation of IV with phenylisothiocyanate at 200° proceeded through the intermediate stages of the initial disubstituted thiourea and the first intramolecular cyclization product to give 1-anilino-8-methoxybenzo(*f*)quinazoline-3(4*H*)-thione (X) directly. The structure of the latter derivative was established by dilute acid hydrolysis to XI. Direct cyclization of the aminonitrile IV to 1-amino-8-methoxybenzo(*f*)quinazoline (XII) was achieved with hot formamide. Reaction of IV with ethyl orthoformate gave the expected ethoxymethyleneamino derivative XIII which upon treatment with ethanolic ammonia cyclized in the normal fashion[11] to XII. An attempt to convert IV to the 1(2*H*)-thione derivative by the sodium hydrosulfide–pyridine method[12] failed, probably because of the effect of the MeO grouping in reducing the electrophilic character of the 1-cyano grouping.

[6a] cf. V. P. Mamaev and V. F. Sedova, *Khim. Geterots Soed.* 787 (1965); *Index Chemicus* 62577 (1966). [b] E. J. Modest, S. Chatterjee and H. Kangur, *J. Org. Chem.* **27**, 2708 (1962).

[7] E. C. Taylor and Y. Shvo, Abstracts of Papers, 152nd Meeting, ACS No. 44, Sect. P. New York, N.Y. September (1966).

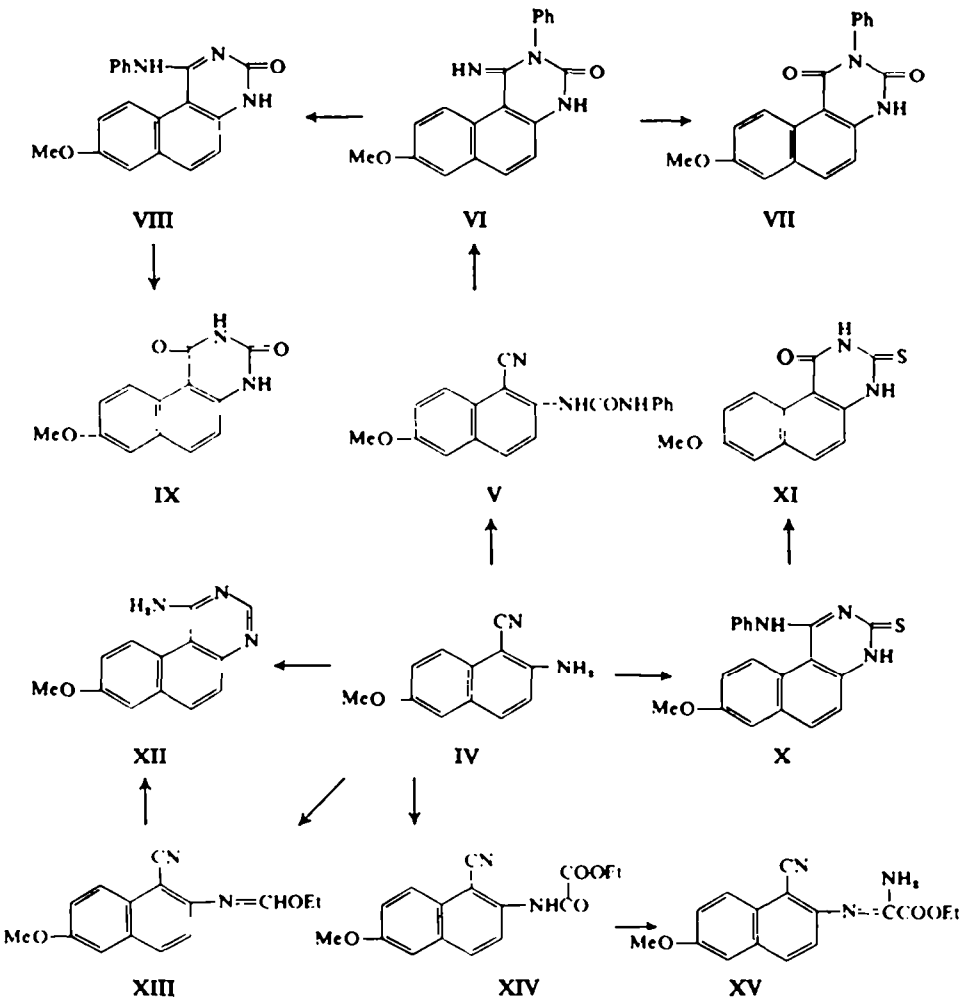
[8] See Ref. 1 for a complete bibliography of work from this laboratory dealing with *o*-aminonitriles in heterocyclic synthesis.

[9] Modest *et al.* (Ref. 5*a–c*) employed 1-cyano-2-naphthylamine as their starting material for the preparation of benzo(*f*)quinazoline derivs.

[10] For an analogous sequence of reactions carried out on anthranilonitrile, see E. C. Taylor and R. V. Ravindranathan, *J. Org. Chem.* **27**, 2622 (1962).

[11] cf. E. C. Taylor and R. W. Hendess, *J. Am. Chem. Soc.* **87**, 1995 (1965).

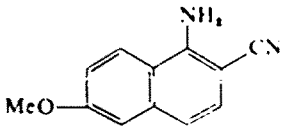
[12] E. C. Taylor, A. McKillop and S. Vromen, *Tetrahedron* **23**, 885 (1967).



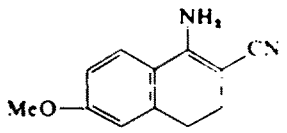
Condensation of IV with diethyl oxalate in ethanol containing potassium methoxide gave the ethoxalyl derivative XIV. This was successfully converted with diazomethane followed by alcoholic ammonia into the urethane XV, but subsequent intramolecular cyclization to the desired 1-amino-3-carboethoxy-8-methoxybenzo(*f*)quinazoline was not observed. Stronger alkaline cyclization conditions (sodium methoxide in DMF) likewise failed to effect cyclization; we attribute this cyclization failure, as well, to the reduced electrophilicity of the 1-cyano grouping.

Further transformations of the aminonitrile IV to benzo(*f*)quinazoline derivatives were discontinued when recent reports of closely related efforts[5] came to our attention.

Preparation of derivatives of the isomeric benzo(*h*)quinazoline system by analogous methods would have required the intermediacy of 2-cyano-6-methoxy-1-naphthylamine (XVI). Rather than attempt the preparation of this previously undescribed intermediate, we chose to consider the preparation of the corresponding 3,4-dihydro compound XVII which would have led to related pyrimethamine analogs with an



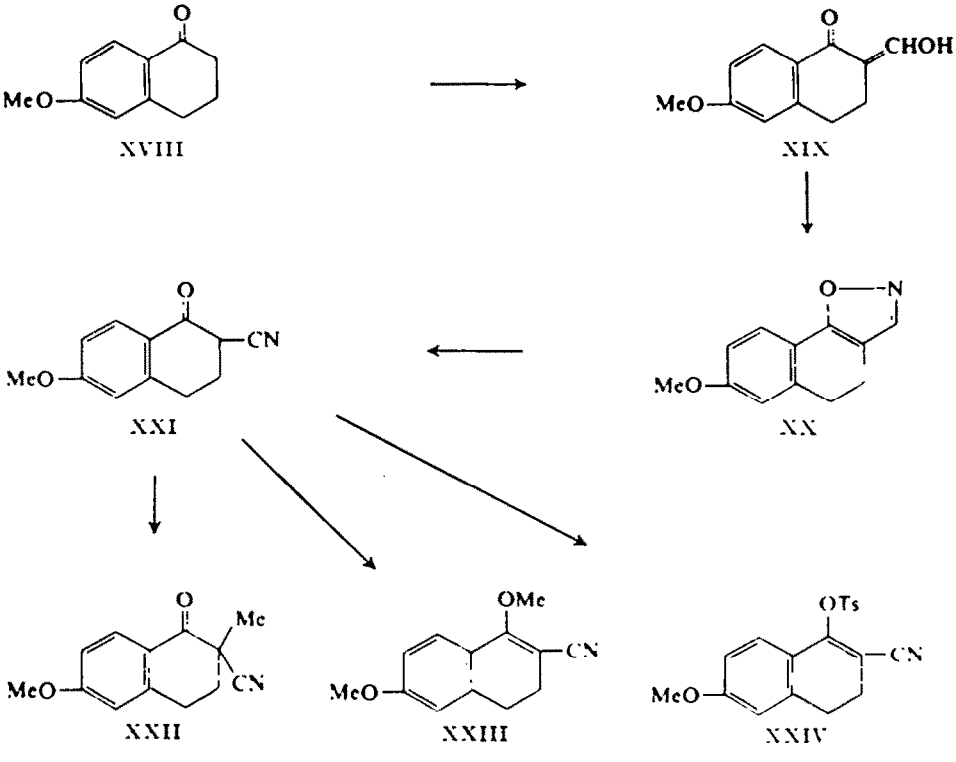
XVI



XVII

ethano bridge (*vide supra*). Although all efforts thus far to prepare the desired aminonitrile intermediate XVII have been unsuccessful on a preparative scale, a number of compounds were prepared which proved to be useful in subsequent conversions to derivatives of the desired dihydrobenzo(*h*)quinazoline system III. These syntheses, as well as our unsuccessful efforts to prepare XVII, are described below.

We chose as our starting material for the attempted preparation of XVII the commercially available 6-methoxy-1-tetralone (XVIII).[13] Reaction with ethyl formate in ethanol solution in the presence of sodium methoxide gave the hydroxymethylene derivative XIX[14] which was converted in high yield with hydroxylamine hydrochloride in glacial acetic acid to 7-methoxy-4,5-dihydronaphtho(2,1-*d*)isoxazole (XX).[15] This



XVIII XIX XXI XX XXII XXIII XXIV

[13] Supplied by Millmaster Chemical Corporation, 99 Park Avenue, New York 16, N.Y.
[14] W. S. Johnson, J. M. Anderson and W. E. Shelberg, *J. Am. Chem. Soc.* **66**, 218 (1944).
[15] D. K. Banerjee, S. Chatterjee, C. N. Pillai and M. V. Bhatt, *J. Am. Chem. Soc.* **78**, 3769 (1956).

was ring-opened smoothly with sodium methoxide in absolute methanol to 2-cyano-6-methoxy-1-tetralone (XXI).[15] Although 2-cyanocyclohexanone[16] and related cycloalkanones[17] have been converted with ammonium formate or with aqueous ammonium carbonate to the corresponding 1-amino-2-cyano-1-cycloalkenes, analogous conditions failed to have any effect on XXI. This compound was also recovered unchanged after heating at 100° with aqueous ammonium carbonate, and even upon treatment with liquid ammonia.

Since the unsuccessful reactions above might be attributable, at least in part, to the acidity of the 2-hydrogen,[18] conversion of XXI to the corresponding vinyl ether was considered. Methylation with methyl iodide in sodium ethoxide is known to result in C-methylation to give 2-methyl-2-cyano-6-methoxy-1-tetralone (XXII),[15,19] but methylation with diazomethane led to the desired 1,6-dimethoxy-2-cyano-3,4-dihydronaphthalene (XXIII). Surprisingly, this compound also proved to be inert to ammonia in hot chloroform, ammonium hydroxide in refluxing ethanol, and even to hydrazine in refluxing methanol. When XXIII was heated for prolonged periods in methanol containing hydrazine and hydrochloric acid, a mixture of unchanged XXIII and the α-cyanoketone XXI was obtained; no trace of the desired 1-hydrazino derivative was discernible.

It seemed reasonable to expect that the tosyl ether XXIV might be an attractive alternative to the methyl vinyl ether XXIII in attempted displacement reactions with amines.[20] Treatment of XXI with tosyl chloride in pyridine gave the desired intermediate XXIV but it, too, proved inert to ammonium hydroxide in refluxing ethanol and also to anhydrous ammonia in refluxing ethanol for periods up to 18 hr. When XXIV was heated for 21 hr with ammonium formate, only a mixture of unchanged XXIV and the α-cyanoketone XXI was obtained.

Alternative approaches to the desired aminonitrile XVII were then explored. It has recently been reported[21] that treatment of indazole with sodamide in liquid ammonia gives *o*-aminobenzamidine, apparently *via* initial abstraction by amide ion of the 3-proton, followed by ring-opening, with nitrogen-nitrogen cleavage, to give

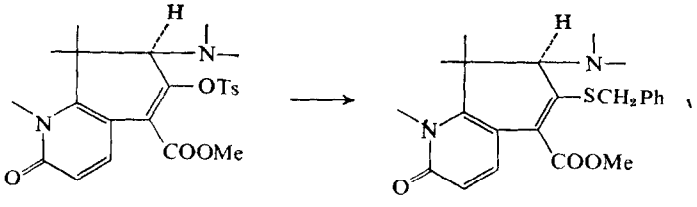
[16] K. von Auwers, T. Bahr and E. Frese, *Liebigs Ann.* **441**, 68 (1925).

[17] T. Sheradsky and P. L. Southwick, *J. Org. Chem.* **30**, 194 (1965).

[18] Both steric (peri-hydrogen) and electronic (a *para*-situated MeO group) probably contribute to the decreased carbonyl reactivity of XXI.

[19] W. S. Johnson, J. W. Petersen and C. D. Gutsche, *J. Am. Chem. Soc.* **69**, 2942 (1947).

[20] In the synthesis of strychnine (R. B. Woodward, M. P. Cava, W. D. Ollis, A. Hunger, H. U. Daeniker and K. Schenker, *Tetrahedron* **19**, 247 (1963)), treatment of the enol-tosylate (partial structure (i)) with sodium benzyl mercaptide resulted in smooth displacement of the tosylate group and generation of the thioenol ether (partial structure (ii)).

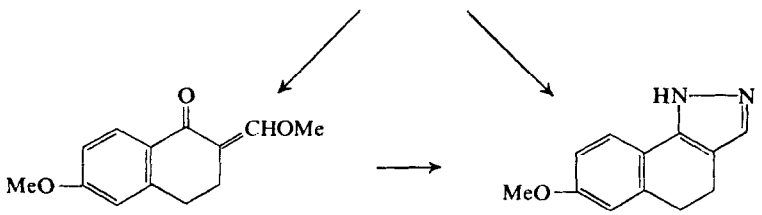


i ii

[21] A. M. Simonov and B. K. Martsokha, *Khim. Geterots Soed* **5**, 774 (1965); *Index Chemicus* **20**, 62572 (1966).

anthranilonitrile, which then reacts further with amide ion. In order to explore the possibility that a similar nitrogen-nitrogen cleavage might be observed on treatment of the benz(*g*)indazole XXVI with sodium hydride, we prepared XXVI by treatment of the hydroxymethylene compound XIX with hydrazine in refluxing ethanol. When XIX was dissolved in anhydrous methanol, a drop of concentrated sulfuric acid added, and the reaction mixture was then diluted with ice-water,[19] an almost instantaneous and quantitative separation of the methoxymethylene derivative XXV occurred; subsequent treatment of this compound with hydrazine likewise gave the benzindazole XXVI. Unfortunately, the action of sodium hydride in refluxing benzene upon XXVI was ineffective and only unchanged starting material could be recovered.

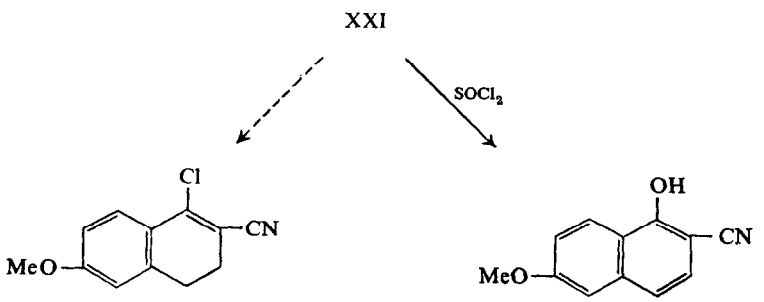
XIX



XXV XXVI

Although displacement of methoxyl or tosyl groups from the intermediates XXIII and XXIV with ammonia was not observed, one more attempt to prepare an intermediate perhaps susceptible to nucleophilic displacement to give the desired aminonitrile XVII was made. 2-Cyano-6-methoxy-1-tetralone (XXI) was treated with thionyl chloride in benzene in an attempt to prepare the vinyl chloride derivative XXVII, but 2-cyano-6-methoxy-1-naphthol was formed in quantitative yield.

XXI

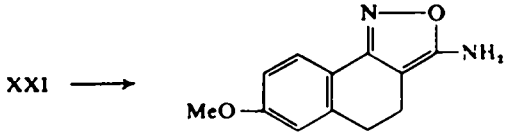


XXVII XXVIII

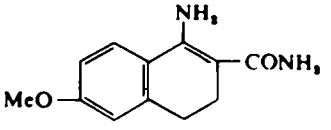
Successful introduction of an amino function at position 1 of the 3,4-dihydronaphthalene system present in XVII was finally achieved as follows. The α-cyanoketone XXI was treated with hydroxylamine hydrochloride in aqueous sodium hydroxide to give the aminoisoxazole XXIX.[22] Zinc and acetic acid reduction of this compound resulted in hydrogenolysis of the labile nitrogen-oxygen bond to give

[22] cf. A. Obregia, *Liebigs Ann.* **266**, 329 (1899).

1-amino-2-carboxamido-6-methoxy-3,4-dihydronaphthalene (XXX).[23] Attempts to dehydrate this aminoamide to the desired aminonitrile XVII are currently in progress.

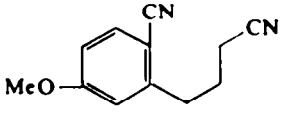


XXIX

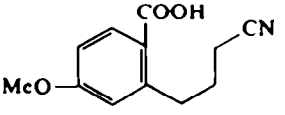


XXX

Intramolecular base-catalyzed cyclization of α,ω-dinitriles to give 1-amino-2-cyanocycloalkenes is a well-known reaction (the Thorpe-Ziegler condensation);[24] application of this scheme to the preparation of the desired aminonitrile XVII would require the intermediacy of 2-(3-cyanopropyl)-4-methoxybenzonitrile (XXXI). Since



XXXI



XXXII

2-cyanocyclohexanone has been reported to undergo alkaline cleavage under selected conditions in almost quantitative yield to give ε-cyanohexanoic acid,[25] attempts were made to subject XXI to an analogous alkaline cleavage in the expectation that the initial hydrolysis product (the substituted benzoic acid XXXII) should be capable of conversion to the desired dinitrile XXXI by conventional operations. The α-cyanoketone XXI, however, proved once again to be unexpectedly unreactive. It was recovered unchanged after refluxing for periods up to 12 hr in ethanolic sodium hydroxide (conditions much more severe than required for the alkaline cleavage of 2-cyanocyclohexanone itself). When the heating time was extended to 72 hr, a complex mixture of hydrolysis products was obtained which consisted of 2-carboxamido-6-methoxy-1-tetralone, 6-methoxy-1-tetralone (XVIII), unchanged XXI and trace amounts of base soluble products which did not, however, contain a nitrile grouping.[26]

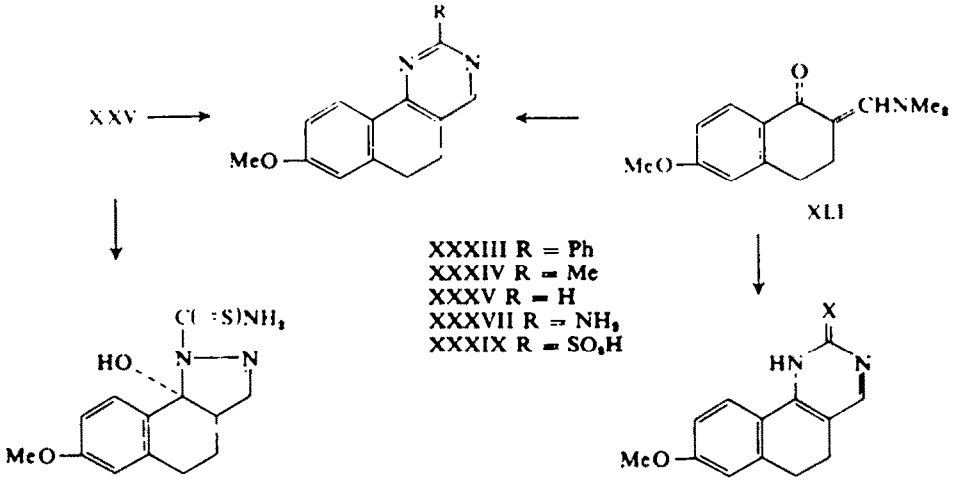
[23] cf. G. Shaw and G. Sugowdz, *J. Chem. Soc.* 665 (1954). It should be noted that Zn–AcOH appears to be specific for the hydrogenolysis of the N—O bond in XXIX; catalytic reduction using a variety of catalysts and conditions led only to difficultly separable mixtures of products.

[24a] J. F. Thorpe, *J. Chem. Soc.* 1901 (1909); [b] K. Ziegler, H. Oberle and H. Ohlinger, *Liebigs Ann.* **504**, 94 (1933).

[25] K. von Auwers, T. Bahr and E. Frese, *Liebigs Ann.* **441**, 54 (1925).

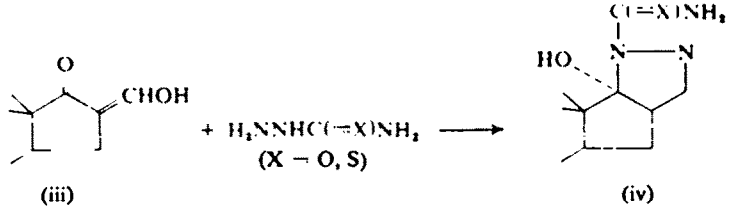
[26] The alkaline cleavage of cyclic α-cyanoketones has been studied in some detail by W. S. Johnson and W. E. Shelberg, *J. Am. Chem. Soc.* **67**, 1754 (1945). While 2-cyano-1-tetralone can be cleaved in good yield to give *o*-(3-carboxypropyl)benzoic acid, 5-methoxy-1-hydrindanone under the same conditions gave only a poor yield of 2-(2-carboxyethyl) 4-methoxybenzoic acid.

The synthesis of a number of benzo(*h*)quinazolines from the foregoing intermediates was achieved as follows. 2-Phenyl and 2-methyl-8-methoxybenzo(*h*)quinazoline (XXXIII and XXXIV respectively), as well as the 2-unsubstituted derivative XXXV, were prepared by treatment of XXV with benzamidine, acetamidine, and formamidine respectively. Treatment of XXV with thiosemicarbazide in ethanol solution gave a homogeneous product, but it was not the expected benzo(*h*)quinazoline and its structure, while not rigorously established, appears to be XXXVI.[37]



Several additional derivatives of the benzo(*h*)quinazoline system were prepared from 2-dimethylaminomethylene-6-methoxy-1-tetralone (XLI), which was formed from 6-methoxy-1-tetralone by reaction with bis(dimethylamino)methoxymethane.[38] Treatment of XLI with guanidine and with thiourea gave the expected derivatives XXXVII and XXXVIII, but urea gave a complex reaction which has not yet been unravelled. The desired 8-methoxy-5,6-dihydrobenzo(*h*)quinazoline-2(1*H*)-one(XL) was therefore prepared from the corresponding thione XXXVIII by oxidation with alkaline hydrogen peroxide to the 2-sulfinic acid XXXIX, followed by aqueous alkaline hydrolysis at steam bath temperature. The reaction of XLI with thiosemicarbazide

[37] It has recently been shown (R. E. Schaub, J. H. van den Hende and M. J. Weiss, *J. Org. Chem.* **30**, 2234 (1965)) that treatment of 17-keto-16-hydroxymethylene steroids (partial structure (iii) with semicarbazide or thiosemicarbazide leads to an anomalous reaction with the formation of hydroxycarbamoyl pyrazolines (partial structure (iv)).



[38] H. Bredereck, F. Effenberger and G. Simchen, *Chem. Ber.* **98**, 1078 (1965).

gave the same product (XXXVI) as was formed starting with XXV; however, only complex mixtures were obtained upon treatment of XLI with semicarbazide or aminoguanidine.

The majority of the compounds prepared in the present study have been submitted to the Smith Kline and French Laboratories for pharmacological evaluation; results of this screening will be published independently.

EXPERIMENTAL[19]

1-Phenyl-3-(6-methoxy-1-cyano-2-naphthyl)urea (V)

A mixture of 5 g 2-amino-1-cyano-6-methoxynaphthalene[7] and 3·3 g phenyl isocyanate in 125 ml xylene was heated under reflux for 5 hr. A colorless solid separated slowly from the refluxing soln. The reaction mixture was cooled, filtered, the collected solid washed with hot xylene followed by pet. ether and recrystallized from aqueous DMF to give 7·2 g (90%). The product melted at 240–244°, resolidified, and then remelted at 290–295°. (Found: C, 71·64; H, 4·75; N, 12·98. Calc. for $C_{19}H_{15}N_3O_2$: C, 71·91; 4·76; N, 13·24%.)

1-Imino-2-phenyl-8-methoxy-1,2-dihydrobenzo(f)quinazoline-3(4H)-one (VI)

A suspension of 4·8 g 1-phenyl-3-(6-methoxy-1-cyano-2-naphthyl)urea in 73 ml 0·05M MeONa in MeOH was heated under reflux with stirring for 16 hr. The solvent was removed under reduced press, 100 ml water was added to the residue, and the resulting soln was brought to pH 7 with AcOH. The solid which separated was collected by filtration and washed with water; yield 4·0 g (88%). Recrystallization from hot nitrobenzene gave a pale yellow powder, m.p. 334–336° dec. The IR spectrum of the product failed to show a nitrile band, indicating that complete cyclization had occurred. (Found: C, 71·66; H, 4·81; N, 13·16. Calc. for $C_{19}H_{15}N_3O_2$: C, 71·91; H, 4·76; N, 13·24%.)

2-Phenyl-8-methoxybenzo(f)quinazoline-1,3(2H,4H)-dione (VII)

This was prepared by hydrolysis of VI by heating under reflux for 2 hr with 10% HCl aq. Recrystallization of the crude product from EtOH gave colorless crystals, m.p. 320–325° dec. (Found: N, 8·87. Calc. for $C_{19}H_{14}N_2O_3$: N, 8·80%.)

1-Anilino-8-methoxybenzo(f)quinazoline-3(4H)-one (VIII)

A soln of 1·0 g 1-imino-2-phenyl-8-methoxy-1,2-dihydrobenzo(*f*)quinazoline-3(4*H*)-one in 15 ml nitrobenzene was heated under reflux for 20 min, cooled and the fine yellow needles collected by filtration; yield, 0·75 g (75%), m.p. 336–340° dec. The analytical sample was prepared by recrystallization from hot nitrobenzene and melted at 340–344° dec. (Found: C, 71·79; H, 4·67; N, 13·11. Calc. for $C_{19}H_{15}N_3O_2$: C, 71·91; H, 4·76; N, 13·24%.)

8-Methoxybenzo(f)quinazoline-1,3(2H,4H)-dione (IX)

This was prepared by heating 0·50 g of the above VIII for 4·5 hr in 10% HCl aq. The cooled soln was filtered and the collected solid washed with water and recrystallized from hot DMF to give 0·28 g (78%) m.p. 355–360° dec. (Found: C, 64·63; H, 4·38; N, 11·70. Calc. for $C_{13}H_{10}N_2O_3$: C, 64·46; H, 4·16; N, 11·57%.)

1-Anilino-8-methoxybenzo(f)quinazoline-3(4H)-thione (X)

A mixture of 1·98 g 2-amino-1-cyano-6-methoxynaphthalene and 1·48 g phenyl isothiocyanate was heated in a Wood's metal bath. A vigorous exothermic reaction ensued when the bath reached 200°; the melt resolidified at approximately 215°. The resulting solid was heated at 215–220° for a period of 3 hr and then cooled, pulverized, and digested twice with boiling AcOEt to give 1·90 g (74%) of a yellow-brown solid, m.p. 297–303° dec. The IR spectrum of the crude product failed to reveal the

[19] We are indebted for the microanalyses to G. Robertson, Florham Park, N.J. and to the Spang Microanalytical Laboratories, Ann Arbor, Michigan. All m.ps are uncorrected. IR spectra were determined by the Nujol mull technique using a Perkin–Elmer Model 237B spectrophotometer.

presence of a nitrile band, thus indicating complete cyclization. The analytical sample was prepared by crystallization from hot nitrobenzene, and melted at 300–304° dec. (Found: C, 68·24; H, 4·67; N, 12·35. Calc. for $C_{10}H_{12}N_2OS$: C, 68·46; H, 4·54; N, 12·61%.)

8-Methoxybenzo(f)quinazoline-1(2H)-one-3(4H)-thione (XI)

This was prepared by heating 0·5 g of the above X in a suspension of 60 ml 10% HCl aq and 10 ml 2-ethoxyethanol for 4·5 hr. The resulting solid was collected by filtration, washed thoroughly with water, and recrystallized from aqueous DMF to give a pale yellow powder, m.p. >360°. (Found: C, 60·24; H, 4·01; N, 10·66. Calc. for $C_{13}H_{10}N_2O_2S$: C, 60·46; H, 3·90; N, 10·85%.)

1-Amino-8-methoxybenzo(f)quinazoline (XII)

Method A. A mixture of 5·5 g 2-amino-1-cyano-6-methoxynaphthalene and 30 ml freshly distilled formamide was heated under reflux for 30 min. The resulting brown soln was cooled and the ppt collected by filtration and washed with EtOH; yield, 3·7 g (58%), m.p. 212–215° dec. The analytical sample was prepared by recrystallization from hot nitrobenzene and melted with dec at 213–215°. (Found: C, 69·19; H, 5·02; N, 18·56. Calc. for $C_{13}H_{11}N_3O$: C, 69·32; H, 4·92; N, 18·66%.)

Method B. A mixture of 3·0 g 2-amino-1-cyano-6-methoxynaphthalene and 25 ml ethyl orthoformate was heated under reflux overnight, the hot soln filtered, and the filtrate cooled to 0°. The pale brown needles of 1-cyano-2-ethoxymethyleneamino-6-methoxynaphthalene were collected by filtration and washed with dry ether to give 3·0 g (78%), m.p. 113–116°. Recrystallization from $HCCl_3$–heptane gave colorless needles, m.p. 114–116°. (Found: C, 70·79; H, 5·70; N, 10·97. Calc. for $C_{15}H_{14}N_2O_2$: C, 70·85; H, 5·55; N, 11·02%.)

Refluxing the above 2-ethoxymethyleneamino deriv with ethanolic ammonia (saturated at 0°) gave in 92% yield 1-amino-8-methoxybenzo(f)quinazoline, identical with the material prepared by Method A above.

1-Cyano-2-ethoxalylamino-6-methoxynaphthalene (XIV)

To a soln of 0·6 g K metal dissolved in 150 ml dry EtOH was added 2·9 g diethyl oxalate followed by 2·4 g 2-amino-1-cyano-6-methoxynaphthalene. The resulting suspension was stirred at room temp overnight, neutralized with AcOH, diluted with 50 ml water, and the resulting solid collected by filtration and washed with water followed by EtOH and ether; yield 3·4 g (86%), m.p. 172–175°. The product was obtained in the form of long yellow needles upon recrystallization from AcOEt. (Found: C, 64·23; H, 4·80; N, 9·43. Calc. for $C_{16}H_{14}N_2O_4$: C, 64·42; H, 4·73; N, 9·39%.)

A soln of 1·0 g of XIV in 70 ml anhyd THF and 20 ml diazomethane (excess) in ether was allowed to stand overnight at room temp, the solvents removed *in vacuo* and 5 ml EtOH saturated with ammonia added to the residue. After 1·5 hr at room temp, the crystalline solid which separated was collected by filtration; yield, 0·25 g, m.p. 275–278°. Its IR spectrum supported the formulation of this product as XV (3200–3400 cm^{-1} (primary —NH_2), 2210 cm^{-1} (nitrile,) 1685 cm^{-1} (unsaturated ester)). However, attempts to effect intramolecular cyclization with MeONa in DMF at 70° resulted only in cleavage to regenerate 2-amino-1-cyano-6-methoxynaphthalene.

1,6-Dimethoxy-2-cyano-3,4-dihydronaphthalene (XXIII)

An ethereal soln of diazomethane (excess) was added to a stirred suspension of 5·0 g 2-cyano-6-methoxy-1-tetralone[16,18] in ether which was held at 0° in an ice-bath. The mixture was stirred at 0° for 10 hr and at room temp for a further 6 hr, after which time all of the suspended solid had passed into soln. Removal of the ether solvent under reduced press left a pale yellow oil which rapidly solidified to give 5·6 g crude product, m.p. 55–59°. This material defied recrystallization because of its extreme solubility in all organic solvents, and was thus best purified by distillation (b.p. 145–146°/0·05 mm) to give 5·1 g (95%) of a colorless oil which rapidly solidified; m.p. 58–60°. The compound gradually turned yellow on exposure to light. (Found: C, 72·52; H, 6·17; N, 6·33. Calc. for $C_{13}H_{13}NO_2$: C, 72·54; H, 6·09; N, 6·51%.)

1-Tosyloxy-2-cyano-6-methoxy-3,4-dihydronaphthalene (XXIV)

A soln of 5·0 g *p*-toluenesulfonylchloride and 5·0 g 2-cyano-6-methoxy-1-tetralone in 75 ml anhyd pyridine was allowed to stand for 48 hr at room temp. The resulting black soln was poured

with stirring into 300 ml ice-water. The ppt was collected by filtration, washed with water, dried, and recrystallized from EtOH (charcoal) to give 4·2 g (50%) of pale yellow needles, m.p. 138–140°. (Found: C, 64·16; H, 4·85; N, 3·83. Calc. for $C_{16}H_{17}NO_4S$: C, 64·22; H, 4·82; N, 3·94%.)

2-Methoxymethylene-6-methoxy-1-tetralone (XXV)

To a gently refluxing soln of 1·0 g 2-hydroxymethylene-6-methoxy-1-tetralone[19] in 45 ml MeOH was added 1 drop of conc H_2SO_4, the mixture refluxed for a further 2 min and then poured with stirring into 100 ml ice-water. The colorless solid which separated was collected by filtration, washed with water, and dried to give 0·98 g (97%) colorless needles, m.p. 89–94°. The m.p. was raised to 93–95° by recrystallization from pet. ether (b.p. 60–80°). (Found: C, 71·44; H, 6·46. Calc. for $C_{13}H_{14}O_3$: C, 71·54; H, 6·47%.)

7-Methoxy-4,5-dihydrobenzo(g)indazole (XXVI)

Method A. A mixture of 5·0 g 2-methoxymethylene-6-methoxy-1-tetralone and 5 ml 85% hydrazine hydrate in 50 ml EtOH was heated under reflux for 2 hr. The original deep red color rapidly discharged to give a pale yellow soln. The cooled reaction mixture was poured into 200 ml ice-water and the ppt (colorless) collected by filtration, washed with water, and dried to give 4·73 g (96%), m.p. 164–166°. Recrystallization from aqueous EtOH gave colorless needles with no change in m.p. (Found. C, 72·15; H, 6·05; N, 13·95. Calc. for $C_{13}H_{12}N_2O$: C, 71·98; H, 6·04; N, 13·99%.)

Method B. A mixture of 2·0 g 2-dimethylaminomethylene-6-methoxy-1-tetralone (see below) and 0·5 g 85% hydrazine hydrate in 50 ml EtOH was stirred at room temp for 2 hr. Addition of 100 ml ice-water precipitated a colorless solid which was recrystallized as described above to give 1·6 g (100%) colorless needles, m.p. 164–166°, identical with the product prepared by Method A.

2-Cyano-6-methoxy-1-naphthol (XXVIII)

A mixture of 2·0 g 2-cyano-6-methoxy-1-tetralone and 2·0 g $SOCl_2$ in 50 ml anhyd benzene was heated on the steam bath for 2 hr, concentrated under reduced press and the residue poured into 100 ml ice-water. The ppt (green) was collected by filtration, washed with water, dried and recrystallized from aqueous DMSO to give 1·9 g (99%) colorless needles, m.p. 233–235° (dec). (Found: C, 72·28; H, 4·36; N, 6·96. Calc. for $C_{13}H_9NO_2$: C, 72·35; H, 4·55; N, 7·03%.)

3-Amino-7-methoxy-4,5-dihydroisoxazolo(3,4-b)naphthalene (XXIX)

To a stirred soln of 2·01 g (0·01 mole) 2-cyano-6-methoxy-1-tetralone in an excess 0·5N NaOH was added 1·39 g (0·02 mole) hydroxylamine hydrochloride. A colorless solid slowly separated from the soln and after 72 hr stirring, the solid was filtered off, washed with water, and dried. The resulting 0·6 g (40%) colorless powder, m.p. 145–150°, was recrystallized from aqueous EtOH to give long colorless needles, m.p. 152–154°. (Found: C, 66·63; H, 5·60; N, 12·75. Calc. for $C_{13}H_{12}N_2O_2$: C, 66·65; H, 5·59; N, 12·96%.)

1-Amino-2-carboxamido-6-methoxy-3,4-dihydronaphthalene (XXX)

A mixture of 2·0 g 3-amino-7-methoxy-4,5-dihydroisoxazolo(3,4-*b*)naphthalene and 0·6 g Zn dust in 150 ml glacial AcOH was heated under reflux for 2 hr. The warm reaction mixture was poured into 500 ml water and the ppt (brown) collected by filtration, washed well with water, dried and recrystallized from aqueous acetone to give 1·5 g (75%) colorless needles, m.p. 250–254°. (Found: C, 66·15; H, 6·25; N, 12·59. Calc. for $C_{13}H_{14}N_2O_3$: C,66·03; H, 6·47; N, 12·84%.)

2-Phenyl-8-methoxy-5,6-dihydrobenzo(h)quinazoline (XXXIII)

A soln of 0·02 mole benzamidine (from 3·13 g benzamidine hydrochloride and 0·46 g Na in 25 ml anhyd MeOH) was added to a soln of 4·36 g (0·02 mole) 2-methoxymethylene-6-methoxy-1-tetralone in 15 ml MeOH, and the reaction mixture was heated under reflux with stirring for 4 hr. The cooled mixture was then poured into ice-water. The pale yellow oil which first precipitated solidified upon scratching and was filtered off, washed with water, and recrystallized from 1:10 aqueous EtOH to give 5·33 g (93%) small colorless clusters of needles, m.p. 92–94°. (Found: C, 79·13; H, 5·75; N, 9·71. Calc. for $C_{19}H_{16}N_2O$: C, 79·14; H, 5·59; N, 9·72%.)

2-Methyl-8-methoxy-5,6-dihydrobenzo(h)*quinazoline* (XXXIV)

The preparation of this compound was as described for the 2-phenyl deriv, except that the oil which precipitated upon dilution of the reaction mixture with water failed to crystallize. The mixture was therefore extracted with 3 50-ml portions $HCCl_3$, the combined extracts dried over Na_2SO_4, the solvent removed under reduced press and the residual oil distilled (b.p. 172–176°/0·5 mm) to give 3·94 g (87%) of a pale yellow oil which rapidly solidified. The analytical sample was then prepared as pale yellow needles, m.p. 69–71°, by recrystallization from pet. ether (b.p. 40–60°). (Found: C, 74·48; H, 6·50; N, 12·21. Calc. for $C_{14}H_{14}N_2O$: C, 74·31; H, 6·24; N, 12·38%.)

8-Methoxy-5,6-dihydrobenzo(h)*quinazoline* (XXXV)

This was prepared as described for the 2-methyl derivative. The crude oil obtained by $HCCl_3$ extraction was distilled (b.p. 162–170°/0·5 mm) to give 3·79 g (89%) pale yellow oil which rapidly solidified. The analytical sample was obtained as golden yellow needles, m.p. 119–120°, upon recrystallization from heptane. (Found: C, 73·81; H, 5·99; N, 13·24. Calc. for $C_{13}H_{12}N_2O$: C, 73·56; H, 5·70; N, 13·20%.)

1-(Thiocarbonyl)-7-methoxy-1a-hydroxy-4,5-dihydrobenzo(g)*indazole* (XXXVI)

A soln of 2·0 g 2-dimethylaminomethylene-6-methoxy-1-tetralone (see below) and 0·91 g thiosemicarbazide in 75 ml EtOH containing 2 drops 30% NaOH aq was stirred for 2 hr at room temp. Acidification of the reaction mixture with 50% HCl aq precipitated an orange solid which was collected by filtration and recrystallized from aqueous DMF to give 2·0 g (83%) orange needles, m.p. 208–210°. (Found: C, 55·91; H, 5·63; N, 14·86; S, 11·25. Calc. for $C_{13}H_{14}N_2O_2S$: C, 56·31; H, 5·45; N, 15·16; S, 11·53%.) λ_{max}^{EtOH} 227, 280 mμ (ε 16,500, 35,200).

2-Dimethylaminomethylene-6-methoxy-1-tetralone (XLI)

A mixture of 2·0 g 6-methoxy-1-tetralone and 2·0 g bis(dimethylamino)methoxymethane[36] was heated for 4 hr in an oil bath maintained at 100–110°. The resulting deep brown oil was cooled, dissolved in 25 ml EtOH, and the soln stirred into 500 ml ice-cold water. The glistening yellow needles which precipitated were collected by filtration, washed with water, and dried to give 2·71 g crude product. Recrystallization from benzene–pet. ether (b.p. 40–60°) gave 2·51 g (95%) of long yellow needles, m.p. 98–100°.

This compound is rather unstable and develops a brown color after standing for several days, even under N_2. However, recrystallization of a 2·0 g sample of apparently decomposed material (almost black) gave 1·93 g pure XLI, indicating that the deep coloration originated from only a small amount of decomposed material. (Found: C, 70·60; H, 7·58; N, 5·82. Calc. for $C_{14}H_{17}NO_2 \cdot \frac{1}{2}H_2O$: C, 69·97; H, 7·55; N, 5·83%.)

2-Amino-8-methoxy-5,6-dihydrobenzo(h)*quinazoline* (XXXVIII)

2-Dimethylaminomethylene-6-methoxy-1-tetralone (1·80 g, 0·0077 mole) was dissolved in 20 ml dry EtOH and the resulting soln added over a period of 15 min to a refluxing soln of 0·75 g (0·0077 mole) guanidine hydrochloride in 20 ml EtOH containing 1·0 g EtONa (from 0·36 g Na). The reaction mixture was heated under reflux for 4 hr and then poured with stirring into 200 ml ice-water. The glistening crystals which separated were collected by filtration, washed with water, and dried to give 0·97 g (57%) glistening colorless plates, m.p. 165–168°. The product was obtained in the form of colorless needles upon recrystallization from benzene–pet. ether (b.p. 60–80°) without change in the m.p. (Found: C, 68·46; H, 5·81; N, 18·23. Calc. for $C_{13}H_{13}N_3O$: C, 68·70; H, 5·77; N, 18·49%.)

8-Methoxy-5,6-dihydrobenzo(h)*quinazoline-2(1H)-thione* (XXXVIII)

A soln of 2·31 g (0·01 mole) 2-dimethylaminomethylene-6-methoxy-1-tetralone in 20 ml EtOH was added over 15 min to a refluxing soln of 1·52 g (0·02 mole) thiourea in 20 ml EtOH containing 1·0 g EtONa (from 0·36 g Na). The reaction mixture was heated under reflux for 4 hr, the solvent removed by distillation under reduced press, and the residue dissolved in water, heated to reflux, treated with charcoal, and filtered. Acidification of the filtrate and cooling gave a canary yellow solid which was collected by filtration, washed with water and dried; yield, 2·16 g (90%), m.p. 256–260°

(dec). Recrystallization from aqueous DMF gave clusters of yellow needles, m.p. 264–267° (dec). (Found: C, 63·54; H, 5·19; N, 11·60. Calc. for $C_{13}H_{12}N_2OS$: C, 63·92; H, 4·95; N, 11·47%.)

8-*Methoxy*-5,6-*dihydrobenzo*(h)*quinazoline*-2-*sulfinic acid* (XXXIX)

To a cooled soln of 3·0 g 8-methoxy-5,6-dihydrobenzo(*h*)quinazoline-2(1*H*)-thione in 75 ml water and 200 ml EtOH containing 1·5 g NaOH was added, dropwise, a total of 9·6 g 30% H_2O_2 over a period of 20 min. After addition was complete, the ice-bath was removed and the mixture stirred for an additional 4 hr at room temp. Evaporation of the reaction mixture under reduced press resulted in separation of a white solid which was collected by filtration, dried, and recrystallized from DMSO to give 3·1 g (89%) colorless needles, m.p. 345°. (Found: C, 53·09; H, 4·44; N, 9·25. Calc. for $C_{13}H_{12}N_2O_3S.H_2O$: C, 53·06; H, 4·80; N, 9·52%.)

8-*Methoxy*-5,6-*dihydrobenzo*(h)*quinazoline*-2(1*H*)-*one* (XL)

A soln of 2·0 g of the above sulfinic acid in 15 ml 10% NaOH aq was heated on a steam bath for 1 hr, cooled, and the reaction mixture acidified with dil HCl aq. The solid which separated was collected by filtration and recrystallized from aqueous DMSO to give 1·3 g (98%) yellow needles, m.p. 264–265°. (Found: C, 68·54; H, 5·38; N, 12·22. Calc. for $C_{13}H_{12}N_2O_2$: C, 68·41; H, 5·30; N, 12·27%.)