[CONTRIBUTION FROM THE DEPARTMENT OF BIOLOGICAL SCIENCES, STANFORD RESEARCH INSTITUTE]

Potential Anticancer Agents.[1] XXXIV. Nonredox Analogs of Riboflavin. I. Model Studies

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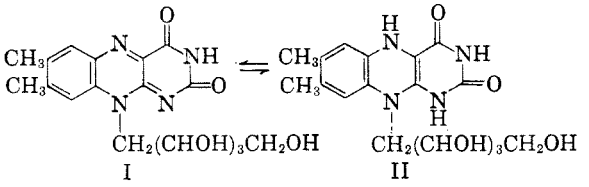
The syntheses of methyl 1,2,3,4-tetrahydro-1,4,4,6,7-pentamethyl-2-oxo-3-quinolinecarboxylate (XVI) and methyl 1,2-dihydro-1,6,7-trimethyl-2-oxo-3-quinolinecarboxylate (XLVI) from 3,4-xylidine (VII) are described. Reaction of XVI with guanidine followed by deamination of the product with nitrous acid gave the desired model compound, 5,10-dihydro-5,5-7,8,10-pentamethylpyrimido[4,5-b]quinoline-2,4(3H,4aH)dione (XXIII). Reaction of XLVI with guanidine afforded 2,10-dihydro-2-imino-7,8,10-trimethylpyrimido[4,5-b]quinoline-4(3H)one (L), which could not be deaminated with nitrous acid.

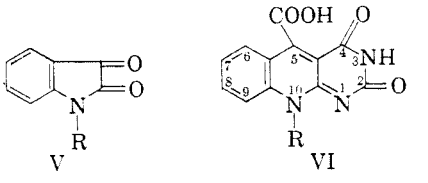
Riboflavin (I), in its cofactor form, owes its biological activity to its ability to accept electrons and be reduced to the dihydro form (II). Modification or elimination of this redox system could be expected to result in compounds that behave as riboflavin antagonists. Thus, dichloroflavin (7,8-dichloro - 10 - ribitylisoalloxazine), in which the methyl groups were replaced by chloro, has a redox potential of $E_0 = -0.095$ volt as compared to riboflavin with a potential of $E_0 = -0.185$. It has been suggested[2] that dichloroflavin is an antagonist because of this difference in redox potential.

Replacement of the N_5-nitrogen of dihydroriboflavin (1,5-dihydro-7,8-dimethyl-10-ribitylisoalloxazine) by a methylene group, as in III (R = ribityl), would be expected to have a profound effect



on the redox potential as compared to riboflavin. Similarly, replacement of the N_5-nitrogen of dihydroriboflavin by an isopropylidene group (IV. R = ribityl) fixes the molecule in the dihydro form, thus eliminating the redox system completely. Although IV is derived from dihydroflavin (II) rather than from riboflavin, the redox enzyme system employing riboflavin coenzymes utilizes both the oxidized and reduced forms; thus analogs of either I or II should be effective antagonists.

Little is known about the pyrimido[4,5-b]-quinolines, especially those substituted on the 10-position. The synthesis of 2,3,4,10-tetrahydro-2,4-dioxopyrimido[4,5-b]quinoline-5-carboxylic acid (VI. R = H) and 2,3,4,10-tetrahydro-10-methyl-2,4 - dioxopyrimido[4,5 - b]quinoline - 5 - carboxylic acid (VI. R = CH_3) starting with barbituric acid and isatin (V. R = H) or *N*-methylisatin (V. R = CH_3) has been described by King, *et al.*[3] They reported that the 5-carboxyl derivative of VI (R =



H) was extremely resistant to decarboxylation, thus negating the use of this approach for the synthesis of compounds such as III.

In order to gain more information about this ring system, the 10-methyl group was substituted for the 10-ribityl to obviate any complications introduced by the sugar moiety in the evaluation of a synthetic path to III and IV. The attempted synthesis of these model compounds (III. R = CH_3, and IV. R = CH_3) is the subject of this paper.

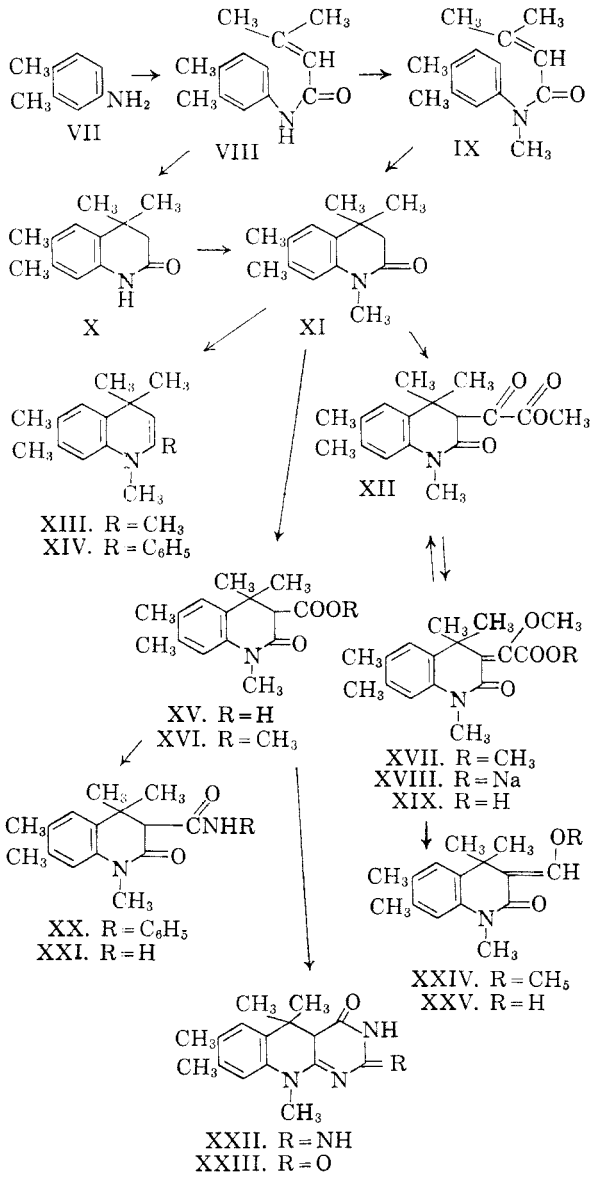
3-Methylcrotonoyl chloride, when treated with 3,4-xylidine (VII) in the manner described[4] for aniline and *o*- and *p*-toluidine, gave 3-methyl-3′,4′-crotonoxylidide (VIII) in 84% yield. *N*-Methylation of the anilide (VIII) with methyl iodide and sodium hydride in *N*,*N*-dimethylformamide proceeded smoothly, the N,3-dimethyl-3′,4′-crotonoxylidide (IX) being isolated as a pure distilled liquid in 84% yield. Cyclization of IX

(1) This work was carried out under the auspices of the Cancer Rhemotherapy National Service Center, National Cancer Institute, National Institutes of Health, Public Health Service, Contract No. SA-43-ph-1892. This paper was presented in part at the 133rd Meeting of the American Chemical Society, San Francisco, Calif., April 16, 1958; see Abstracts, page 27-M. The opinions expressed in this paper are those of the authors and not necessarily those of the Cancer Chemotherapy National Service Center. For the preceding paper in this series, *cf.* W. A. Skinner, H. F. Gram, and B. R. Baker, *J. Org. Chem.*, **25**, 953 (1960).

(2) R. Kuhn, F. Weygand, and E. F. Möller, *Ber.*, **76B**, 1044 (1943).

(3) F. E. King, T. J. King, and G. B. Thompson, *J. Chem. Soc.*, 552 (1948).

(4) J. Colonge and R. Chambard, *Bull. soc. chim. France*, (5), **20**, 982 (1953).



with aluminum chloride in Skellysolve C[5] afforded the crystalline 3,4-dihydro-1,4,4,6,7-pentamethylcarbostyril (XI) in 82% yield,[6] an over-all yield of 69% based on VIII. The alternative route, in which cyclization of VIII with aluminum chloride is followed by *N*-methylation of the resulting carbostyril (X), gave a 47% yield of XI based on VIII. The difference in yield between the two routes was primarily due to a lower yield in the ring closure of VIII as compared to the ring closure of IX.

Treatment of the carbostyril (XI) with diethyl carbonate and sodium hydride in an effort to prepare ethyl 1,2-dihydro-2-oxo-3-quinolinecarboxylate resulted in recovery of unchanged starting material. Condensation of XI with dimethyl oxalate and sodium hydride at 110–115° for four hours gave the crude glyoxalate (XII) as an oil from which a 22% yield of the crystalline 2,4-dinitrophenylhydrazone of XII could be obtained. In an effort to force this condensation to completion, the reaction was run at 135–140° for four hours. The crystalline product obtained from this reaction in 60% yield was not the expected glyoxalate (XII) but the enol ether ester (XVII), as shown by its analysis and infrared spectrum and its failure to form a 2,4-dinitrophenylhydrazone. The infrared spectrum contained a peak at 6.3 μ, assignable to a vinyl double bond, which was not present in the spectrum of the glyoxalate (XII). Hydrolysis of XVII with dilute hydrochloric acid gave an oil which formed, in low yield, a 2,4-dinitrophenylhydrazone identical with that formed from the glyoxalate (XII). Treatment of the enol ether ester with acetic acid, benzoic acid, or toluenesulfonic acid also gave small amounts of the desired glyoxalate (XII) along with unchanged starting material and the enol ether acid (XIX). Saponification of the enol ether (XVII) formed an alcohol-insoluble sodium salt (XVIII), which showed strong carboxylate bands at 6.23 and 7.17 μ in the infrared. Acidification of XVIII gave the crystalline enol ether acid (XIX), whose infrared spectrum still contained the 6.35 μ band of the vinyl double bond. The normal saponification of the enol ether ester (XVII) is in sharp contrast to the behavior of the glyoxalate (XII) toward alkaline conditions, since the latter is not saponified but the oxalyl residue is cleaved with regeneration of the carbostyril (XI).

When the enol ether acid (XIX) was heated above its melting point at 180–190°, gas was evolved over a period of twenty minutes. When gas evolution had ceased, the residue was crystallized from Skellysolve B[5] to give, not the expected aldehyde enol ether (XXIV), but the enol ether ester (XVII) in 30% yield. The mother liquor gave an oil in 35% yield that appeared to consist of a mixture of the desired aldehyde enol ether (XXIV) and free aldehyde (XXV), as shown by its infrared spectrum, which showed enol ether double

(5) Skellysolve B and Skellysolve C are petroleum hydrocarbon fractions with boiling ranges of 62–70° and 88–99°, respectively. They are supplied by Special Products Division, Phillips Petroleum Company, Bartlesville, Okla.

(6) In this ring closure, there was the possibility of obtaining a mixture of two isomers through closure on either the 2- or 6-position of 3,4-xylidine. Since a sharp melting point was obtained after only two recrystallizations and since subsequent reactions gave readily crystallizable products, it can be assumed either that the reaction was oriented mainly in one direction, or that the isomers are readily separable. Steric considerations suggest that closure on the 6-position of the 3,4-xylidine to give the desired carbostyril (XI) would be favored. This prediction is borne out by the presence in the infrared spectrum of a band at 11.32 μ assignable to the out-of-plane vibrations of the isolated hydrogen atoms of a 1,2,4,5-tetrasubstituted benzene ring.[7] The corresponding absorption for the adjacent hydrogen of a 1,2,3,4-tetrasubstituted benzene ring would fall between 11.6 μ and 12.5 μ.[7]

(7) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, John Wiley and Sons, Inc., New York, N. Y., 1954, pp. 67, 68.

bond absorption at 6.22 μ and aldehyde absorption at 3.71 and 5.78 μ. Treatment of the oil with 2,4-dinitrophenylhydrazine gave the dinitrophenylhydrazone derivative of the aldehyde (XXV) in 9% yield. These results could be explained on the basis that some of the enol ether acid (XIX) disproportionated to the enol ether ester (XVII) and the corresponding glyoxylic acid; the latter would be decarboxylated to the aldehyde (XXV). A second possible explanation is that the aldehyde enol ether (XXIV), formed by decarboxylation of the enol ether acid (XIX), transferred its methoxyl group to the enol ether acid (XIX) to generate the aldehyde (XXV) and the enol ether ester (XVII). Heating of the enol ether acid (XIX) in hot quinoline led to a product (or products) whose infrared spectrum showed the presence of carbonyl bands at 5.5 and 5.8 μ, indicative of an anhydride, together with the loss of lactam carbonyl absorption at 6.04 μ, suggesting that some type of skeletal rearrangement had taken place.

An interesting contrast to the reaction of dimethyl oxalate with the carbostyril (XI) was observed in the reaction of diethyl oxalate with XI under the same conditions. The yields of the ethyl glyoxalate corresponding to XII were low and variable (5–25%) and no detectable amount of the enol ethyl ether corresponding to XVII was observed.

The very nature of the sterically hindered system in the carbostyril (XI) that led to limited success in the introduction of a functional group on C_3 by a Claisen condensation was utilized to introduce a carboxyl at C_3 in the following manner. There are many reports on the synthesis of β-oxo acids by a Grignard exchange reaction in sterically hindered methyl ketones.[8] When a similar type of reaction was attempted on XI with ethylmagnesium bromide, no reaction occurred and starting material was recovered unchanged. Treatment of the carbostyril (XI) with methyllithium gave an almost quantitative yield of 1,4-dihydro-1,2,-4,4,6,7-hexamethylquinoline (XIII), the product to be expected from the normal addition of lithium reagent to the carbonyl, with no detectable amount of the desired lithium salt. Fortunately, reaction of XI with phenyllithium gave the lithium salt of XI, which was treated directly with carbon dioxide to give the desired 3-carboxylic acid (XV) in 24% yield together with considerable quantities of unchanged starting material. In a large-scale run, 1,4-dihydro-1,4,4,6,7-pentamethyl-2-phenylquinoline (XIV), the product to be expected from the normal addition of lithium reagent to the carbonyl, could also be detected.

When the carbostyril-3-carboxylic acid (XV) was heated at its melting point of 150°, there was a smooth evolution of carbon dioxide and the carbostyril (XI) could be recovered, thus proving that the introduction of the carboxyl took place at C_3 without any change in the ring system. Refluxing of the 3-carboxylic acid (XV) with thionyl chloride gave the acid chloride of XV as a sirup. This sirup could be treated with aniline to give the crystalline anilide (XX), or with methanol to give the crystalline methyl ester (XVI). A more convenient synthesis of the methyl ester (XVI) involved the treatment of the acid (XV) with methanol and acetyl chloride[9] to give XVI in 77% yield in one step from the acid; the usual types of esterification proceeded poorly.

The synthesis of 5,10-dihydro-5,5,7,8,10-pentamethylpyrimido[4,5-b]quinoline-2,4(3H,4aH)dione (XXIII) was attempted by the fusion of equal amounts of methyl 1,2,3,4-tetrahydro-1,4,4,6,7-pentamethyl-2-oxo-3-quinolinecarboxylate (XVI) and urea. The product isolated from the reaction mixture was the 3-carboxamide (XXI). Condensation of XVI with guanidine hydrochloride and sodium methoxide in refluxing *N*,*N*-dimethylformamide resulted in a 54% yield of 5,10-dihydro-2-imino-5,5,7,8,10-pentamethylpyrimido[4,5-b]-quinoline-4(4aH)one (XXII). Deamination of the 2-imine (XXII) with excess sodium nitrite in acetic acid gave a 45–50% yield of a crude product which appeared to contain two components in approximately equal amounts, as shown by paper chromatography using solvent A.[10] Variation of the reaction conditions with respect to solvent, ratio of sodium nitrite to XXII, temperature, or time failed to give a product that was homogeneous, as shown by paper chromatography. The completeness of the reaction was very easily determined by the visual examination of the paper chromatograms of the crude product of the deamination. The starting material (XXII) appeared as a blue fluorescent spot with R_f 0.82, while the two deamination products appeared as yellow fluorescent spots with R_f values of 0.66 and 0.79, respectively.

Since the deamination of XXII under a variety of conditions appeared to have little or no effect on the formation of XXIII with the exclusion of the unknown by-product, efforts were directed toward the separation of this deamination mixture. The essentially complete insolubility of both components in any of the common solvents eliminated the possibility of purification by recrystallization.

(8) (a) R. Adams and L. O. Binder, *J. Am. Chem. Soc.*, **63**, 2773 (1941); (b) R. Adams, A. W. Anderson, and M. W. Miller, *J. Am. Chem. Soc.*, **63**, 1589 (1941); (c) R. Adams and M. W. Miller, *J. Am. Chem. Soc.*, **62**, 53 (1940); (d) R. C. Fuson, W. O. Fugate, and C. H. Fisher, *J. Am. Chem. Soc.*, **61**, 2362 (1939); (e) E. P. Kohler and R. Baltzly, *J. Am. Chem. Soc.*, **54**, 4015 (1932).

(9) K. Freudenberg and W. Jakob, *Ber.*, **74B**, 1001 (1941).

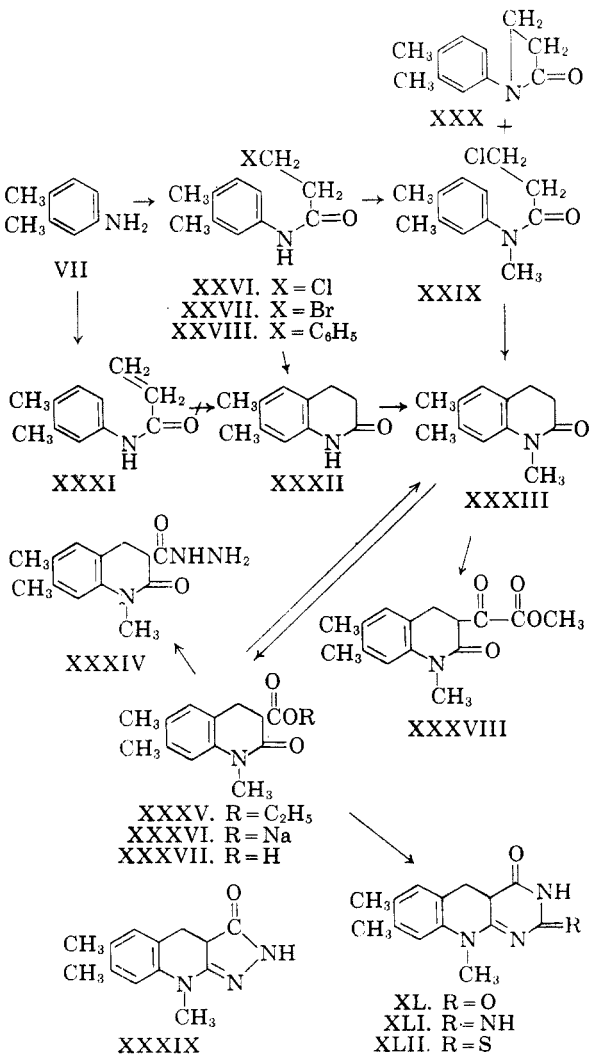
(10) The paper chromatograms were run on Whatman No. 1 paper by the descending technique and spots were located by visual examination under ultraviolet light. The solvent systems used were: A, water saturated butanol; B, butanol–acetic acid–water (4:1:5).

A differential solubility of the two components in concentrated hydrochloric acid made possible the purification of the faster moving of the two components by solution in concentrated hydrochloric acid followed by reprecipitation of the acid-soluble material with water. By this means, a 15% over-all yield of 5,10-dihydro-5,5,7,8,10-pentamethylpyrimido[4,5-b]quinoline-2,4(3H,4aH)-dione (XXIII) hydrochloride was obtained. The hydrochloric acid-insoluble fraction still consisted of a mixture of the two components. Since the by-product was not obtained free of XXIII, its empirical formula could not be determined. Subsequent attempts to repeat this hydrochloric acid separation of XXIII from the by-product were not always successful.

A similar synthetic sequence for the preparation of 5,10-dihydro-7,8,10-trimethylpyrimido[4,5-b]-quinoline-2,4(3H,4aH)dione (XL), starting with xylidine, is outlined in VII→XL. The key intermediate for this synthesis is 3,4-dihydro-1,6,7-trimethylcarbostyril (XXXIII). Many routes to its synthesis from 3,4-xylidine are apparent and a number of these were investigated. Since attempted fusion of 3,4-acryloxylidide (XXXI) with aluminum chloride gave no reaction and starting material was recovered unchanged, the Friedel-Crafts ring closures of the 3-halopropionanilides (XXVI and XXVII) were examined.[11] The condensation of 3,4-xylidine (VII) with 3-chloropropionyl chloride gave the 3-chloropropionamide (XXVI) in 87% yield. Fusion of XXVI with aluminum chloride to give 3,4-dihydro-6,7-dimethylcarbostyril (XXXII) proceeded in a 12% yield. Cyclization of the corresponding 3-bromopropionanilide (XXVII) gave similar yields. Use of Skellysolve C[5] as a solvent in the cyclization of the chloroanilide (XXVI) raised the yield of carbostyril (XXXII) to 27%. Substitution of benzene for Skellysolve C in this reaction[12] led to 3-phenyl-3′,4′-propionoxylidide (XXVIII) instead of the desired carbostyril (XXXII). *N*-Methylation of the dimethylcarbostyril (XXXII) with sodium hydride and methyl iodide in *N*,*N*-dimethylformamide proceeded in 78% yield to 3,4-dihydro-1,6,7-trimethylcarbostyril (XXXIII), a 21% over-all yield from the 3-chloropropionanilide (XXVI).

An effort was made to *N*-methylate the chloroanilide (XXVI) previous to cyclization to the carbostyril, since a similar modification with the 3-methylcrotonanilide (VIII) gave a considerable increase in over-all yield of the carbostyril (XI). One of the by-products to be expected from the methylation of a β-chloroamide such as XXVI is the β-lactam (XXX). That this possible side reaction was a reality was demonstrated by the presence in the infrared spectrum of the *N*-methylation product of a β-lactam carbonyl band at 5.73 μ in addition to the expected amide carbonyl band at 6.04 μ. When the β-chloroanilide (XXVI) was subjected to the basic conditions of the *N*-methylation in the absence of methyl iodide, the β-lactam could be isolated in a pure state. Unfortunately, the mixture of β-lactam (XXX) and trimethylanilide (XXIX) could not be separated by distillation; hence the over-all yield of XXXIII by the cyclization of XXIX as compared to XXVI would not be improved.

Treatment of the trimethylcarbostyril (XXXIII) with dimethyl oxalate and sodium hydride in *N*,*N*-dimethylformamide gave the glyoxalate (XXXV-III), isolated as its 2,4-dinitrophenylhydrazone in 21% yield. There was no evidence for the formation of an enol ether of XXXVIII corresponding to XVII, since the characteristic vinyl



(11) F. Mayer, L. v. Zutphen, and H. Philipps, *Ber.*, **60**, 858 (1927), reported that *N*-methyl-*N*-acrylylaniline failed to cyclize to the dihydrocarbostyril with aluminum chloride. However, they were able to cyclize several *N*-(β-chloropropionyl)anilides.

(12) The use of benzene as a solvent in Friedel-Crafts reactions involving aromatic rings more reactive than benzene has been described by R. Adams, T. A. Geissman, B. R. Baker, and H. M. Teeter, *J. Am. Chem. Soc.*, **63**, 528 (1941).

double bond of the enol ether of XVII at 6.3 μ in the infrared was absent in the crude product.

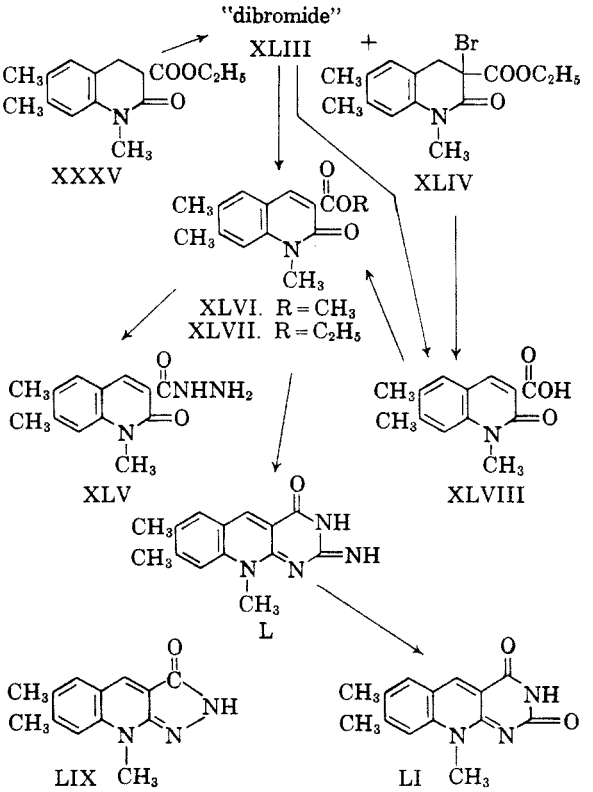
Condensation of XXXIII with diethyl carbonate using sodium hydride in *N,N*-dimethylformamide afforded ethyl 1,2,3,4-tetrahydro-1,6,7-trimethyl-2-oxo-3-quinolinecarboxylate (XXXV) in 42% yield. Saponification of the ethyl ester (XXXV) gave a crystalline sodium salt of the acid (XXXVI) containing the expected carboxylate bands in the infrared. Acidification of the sodium salt afforded the crystalline 3-carboxylic acid (XXXVII), m.p. 155°, which could be decarboxylated at 180° back to the starting trimethylcarbostyril (XXXIII), thus showing that no rearrangements had taken place.

The contrast of reactivities and reaction products between the trimethylcarbostyril (XXXIII) and the pentamethylcarbostyril (XI) is notable. The pentamethylcarbostyril (XI) with its sterically hindered 3-methylene groups, fails to react with diethylcarbonate in contrast to the successful conversion of the trimethylcarbostyril (XXXIII) to its 3-carbethoxy derivative (XXXV). Similarly, the pentamethylcarbostyril (XI) reacted with methyl oxalate at 140° to give the glyoxalate enol ether (XVII), whereas the unhindered trimethylcarbostyril (XXXIII) under the same conditions gave only the expected glyoxalate (XXXVIII) with no detectable amounts of the enol ether.

Reaction of ethyl 3-quinolinecarboxylate (XXXV) with hydrazine in boiling ethyl alcohol gave a crystalline compound whose elemental analysis agreed with that to be expected for the carboxylic acid hydrazide (XXXIV). It is conceivable that the product from the reaction of hydrazine and ethyl ester (XXXV) is a hydrate of the ring-closed pyrazolo[3,4-b]quinoline (XXXIX). It has been assigned the structure of the hydrazide (XXXIV), however, on the basis of the similarity of its ultraviolet absorption spectra to that of the ethyl ester (XXXV).

Attempts to convert the ethyl ester (XXXV) to a pyrimido[4,5-b]-quinoline (XL–XLII) by condensation with urea, guanidine, or thiourea under a large variety of conditions were unpromising; either low yields, intractable mixtures (as shown by paper chromatography), or both were obtained. Part of the difficulty appeared to be the further aromatization of the product(s) to compounds such as L–LI. To avoid the aromatization problem, the condensation of a more fully aromatic ester such as ethyl 1,2-dihydro-1,6,7-trimethyl-2-oxo-3-quinolinecarboxylate (XLVII) with these agents was investigated.

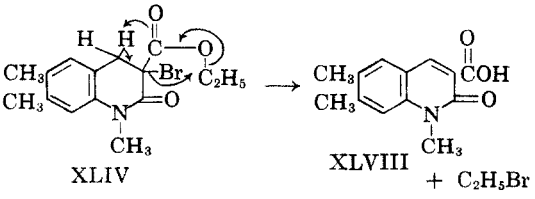
One of the standard methods for aromatization of a compound such as XXXV to XLVII involves bromination, then dehydrohalogenation. Treatment of the ethyl ester (XXXV) with bromine in carbon tetrachloride gave a sirup that could be separated into two components. The minor component proved to be the expected ethyl 3-bromo-1,2,3,4-tetrahydro-1,6,7-trimethyl-2-oxo-3-quinolinecarboxylate (XLIV), obtained in 23% yield. The main



component from the reaction, although crystalline, could not be recrystallized without decomposition and the crude product gave somewhat variable analytical data. The bromine content was consistently high, approaching the value expected for a dibromide of XXXV. Treatment of this 'dibromide' (XLIII) with saturated aqueous sodium bicarbonate gave ethyl 1,2-dihydro-1,6,7-trimethyl-2-oxo-3-quinolinecarboxylate (XLVII) in 29% yield based on the ethyl ester (XXXV). In contrast, aqueous sodium bicarbonate had no effect on the monobromo ester (XLIV) and it could be recovered unchanged.

Thermal decomposition of the monobromo ester (XLIV) proceeded with elimination of the elements of the ethyl bromide to give 1,2-dihydro-1,6,7-trimethyl-2-oxo-3-quinolinecarboxylic acid (XLVIII) in 97% yield.[13] Similarly, the 'dibromide' (XLIII) also gave the aromatic acid (XLVIII). The acid chloride, prepared from the acid (XLVIII)

(13) A possible mechanism for the pyrolysis of the bromo ester (XLIV) is illustrated below:



with thionyl chloride, was treated with either methanol, ethanol, or aniline to give the methyl ester (XLVI) (74% yield), ethyl ester (XLVII) (78% yield), and anilide (61% yield), respectively. The ethyl ester (XLVII) prepared *via* the acid chloride of XLVIII was identical in all respects with the ethyl ester prepared by the sodium bicarbonate treatment of the 'dibromide' (XLIII)

Treatment of the ethyl ester (XLVII) with hydrazine hydrate gave a 95% yield of material which again is believed to be the hydrazide (XLV) rather than the pyrazolo[3,4-b]quinoline (LIX), since its ultraviolet spectrum is very similar to that of the carboxylic acid (XLVIII) and the ethyl ester (XLVII). The pyrazolo[3,4-b]quinoline (LIX) with its longer conjugated system of double bonds would be expected to absorb at longer wave lengths than the acid (XLVIII) or ester (XLVII).

Condensation of the methyl ester (XLVI) with guanidine hydrochloride in methanolic sodium methoxide followed by neutralization with acetic acid gave a material which was homogeneous on paper chromatography in solvent B[10] and which analyzed satisfactorily for the acetate salt of 2,10-dihydro-2-imino-7,8,10-trimethylpyrimido[4,5-b]-quinoline-4(3H)-one (L). Treatment of L, either as the free base or its acetate salt, with nitrous acid under a variety of conditions gave no reaction as shown by paper chromatography[10] and when the attempted deamination was carried out in acetic acid, the acetate salt of L could be recovered unchanged.

The failure of the 2-imine (L) to react with nitrous acid, compared with the facile reaction with nitrous acid of the 2-imine (XXII) and the many other examples of deamination of 2-aminopyrimidines with nitrous acid and/or mineral acid,[14] is surprising and negates the synthesis of compounds of type LI by this route.

EXPERIMENTAL[10,15]

3-Methyl-3',4'-crotonoxylidide (VIII). To a refluxing solution of 60.7 g. (0.50 mole) of 3,4-xylidine (VII) in 100 ml. of benzene was added dropwise with stirring 29.6 g. (0.25 mole) of 3-methylcrotonoyl chloride[16] in 75 ml. of benzene over a period of 80 min. As the addition proceeded, the aniline hydrochloride precipitated. After the addition was complete, the mixture was stirred under reflux for 1 hr. The mixture was cooled, then the hydrochloride was removed by filtration and washed with four 50-ml. portions of benzene. The filtrate was evaporated *in vacuo* and the brown, viscous residue taken up in 450 ml. of 60% ethanol, heated to boiling, treated with Norit, and filtered. The solution was cooled and an oil separated which crystallized. The solid was collected and washed with 150 ml. of cold 1*N* hydrochloric acid, then with 100 ml. of water. The product, after being dried *in vacuo* over Drierite, weighed 43.0 g. (84%). A small sample was recrystallized from 75% methanol for infrared and elemental analysis, m.p. 102–103°; $\lambda_{max(\mu)}^{KBr}$ 3.01 (NH), 6.05 (C=O), 6.13 (C=C), 12.15 (trisubstituted phenyl).

Anal. Calcd. for $C_{13}H_{17}NO$: C, 76.8; H, 8.43; N, 6.89. Found: C, 77.0; H, 8.49; N, 6.84.

3,4-Dihydro-4,4,6,7-tetramethylcarbostyril (X). A stirred suspension of 25 g. (0.12 mole) of 3-methyl-3',4'-crotonoxylidide (VIII) in 250 ml. of Skellysolve C[5] was treated with 50 g. of anhydrous, powdered aluminum chloride. The mixture was stirred under reflux for 3.5 hr. The cooled mixture was decomposed with ice and treated with 20 ml. of 6*N* hydrochloric acid. The white, crystalline solid was collected, washed with 25 ml. of Skellysolve β,[5] and dried *in vacuo* at 60°; yield 17.2 g. (69%), m.p. 178–180°; $\lambda_{max(\mu)}^{KBr}$ 3.11 (NH), 5.89 (lactam C=O), 11.23 (1,2,4,5-tetrasubstituted benzene).

The analytical sample was prepared from a pilot run by two recrystallizations from 60% ethanol with the use of Norit; white crystals, m.p. 176–178°.

Anal. Calcd. for $C_{13}H_{17}NO$: C, 76.8; H, 8.43; N, 6.89. Found: C, 76.9; H, 8.36; N, 6.88.

N,3-Dimethyl-3',4'-crotonoxylidide (IX). To a stirred solution of 10.2 g. (0.05 mole) of 3-methyl-3',4'-crotonoxylidide (VIII) in 85 ml. of *N,N*-dimethylformamide was added 1.30 g. (0.054 mole) of sodium hydride. The mixture was cooled in an ice bath while 8.5 g. (0.06 mole) of methyl iodide was added. After several minutes a white precipitate formed. The mixture was heated on the steam bath for 5 min. The *N,N*-dimethylformamide was distilled under reduced pressure and the residue treated with 50 ml. of chloroform. The resulting mixture was washed with two 50-ml. portions of water. The chloroform was removed under reduced pressure and the product was distilled at 96° (0.025 mm.) (bath temperature 110°); yield 9.0 g. (84%), n_D^{20} 1.5506; $\lambda_{max(\mu)}^{film}$ 6.03 (amide C=O), 6.15 (C=C), 7.32 (CH_3), 12.35 (1,3,4-trisubstituted benzene).

Anal. Calcd. for $C_{14}H_{19}NO$: C, 77.4; H, 8.81; N, 6.45. Found: C, 77.3; H, 8.86; N, 6.30.

3,4-Dihydro-1,4,4,6,7-pentamethylcarbostyril (XI). (A) A stirred mixture of 1.68 g. (0.0083 mole) of 3,4-dihydro-4,4,6,7-tetramethylcarbostyril (X), 0.24 g. (0.01 mole) of sodium hydride, and 2.13 g. (0.015 mole) of methyl iodide in 15 ml. of *N,N*-dimethylformamide was heated at 50–55° for 1 hr. The solvent was removed *in vacuo* and the residue dissolved in 25 ml. of methylene chloride. The resulting solution was washed with 25 ml. of water, dried over magnesium sulfate, then concentrated *in vacuo*. Distillation at 87–91° (0.050 mm.) (bath temperature 110–115°) yielded 1.28 g. (68.2%) of product that solidified in the receiver, m.p. 48–57°. A 1-g. sample was recrystallized from 2.5 ml. of Skellysolve B,[5] to give 0.5 g. of white crystals, m.p. 54–59°; $\lambda_{max(\mu)}^{KBr}$ 5.97 (lactam C=O), 7.41 (CH_3), 11.32 (1,2,4,5-tetrasubstituted benzene).

Anal. Calcd. for $C_{14}H_{19}NO$: C, 77.4; H, 8.81; N, 6.45. Found: C, 77.1; H, 8.92; N, 6.83.

(B) To a stirred suspension of 15 g. (0.11 mole) of anhydrous powdered aluminum chloride in 40 ml. of Skellysolve C[5] was added 6.60 g. (0.030 mole) of *N*,3-dimethyl-3',4'-crotonoxylidide (IX) in 15 ml. of Skellysolve C.[5] The mixture was then heated under reflux on the steam bath for 100 min. The mixture was cooled and decomposed by adding ice. The resulting mixture was treated with 20 ml. of 6*N* hydrochloric acid and the Skellysolve C[5] layer separated. The organic solvent was removed *in vacuo*, leaving 6.76 g. of crude product, m.p. 57–60°. The crude material was recrystallized from 15 ml. of Skellysolve B[5]; yield 4.27 g., m.p. 58–60°. The filtrate was treated with Norit and filtered hot. An additional 1.1 g. of colorless crystals was obtained, m.p. 58–60°. The total yield was 5.37 g. (81.5%).

(14)(a) E. A. Falco and G. H. Hitchings, *Ciba Foundation Symposium on Chemistry of Biology of Pteridines*, Little, Brown and Company, Boston, 1954, p. 183; (b) G. W. Kenner and A. Todd in *Heterocyclic Compounds*, Volume VI, R. C. Elderfield, ed., John Wiley and Sons, Inc., New York, N. Y., 1957, p. 278.

(15) Melting points were taken on a Fisher-Johns apparatus and are uncorrected.

(16) L. I. Smith and V. A. Engelhardt, *J. Am. Chem. Soc.*, **71**, 2671 (1949).

The infrared spectrum was identical with that of the carbostyril prepared by method A.

Methyl 1,2,3,4-tetrahydro-1,4,4,6,7-pentamethyl-2-oxo-3-quinolineglyoxylate (XII). A mixture of 5.0 g. (0.014 mole) of 3,4-dihydro-1,4,4,6,7-pentamethylcarbostyril (XI) and 0.67 g. (0.028 mole) of sodium hydride in 15 g. of dimethyl oxalate and 15 ml. of *N,N*-dimethylformamide was stirred for 4 hr. at 110–115°. The solvent and excess dimethyl oxalate were removed *in vacuo* and the residue was taken up in a solution of 5 ml. of ethanol in 25 ml. of benzene. This solution was diluted with 50 ml. of chloroform and washed with 50 ml. of water. The chloroform solution was dried over magnesium sulfate and concentrated *in vacuo*. A light tan oil weighing 2.65 g. was obtained; $\lambda_{max(\mu)}^{film}$ 5.76 (ester C=O), 6.03 (lactam C=O), 11.30 (1,2,4,5-tetrasubstituted benzene).

A 2,4-dinitrophenylhydrazone was prepared by dissolving 0.523 g. (1.72 mmoles) of the residue of XII in 10 ml. of ethyl alcohol, then adding this solution to a freshly prepared solution of 0.4 g. of 2,4-dinitrophenylhydrazine in 2 ml. of concd. sulfuric acid, 3 ml. of water, and 10 ml. of ethyl alcohol. The resulting solution was stirred and heated on the steam bath at 60° for 2 min., then cooled in an ice bath. The yellow solid that precipitated was removed by filtration and dried; yield 0.185 g. (22.3%). The crude 2,4-dinitrophenylhydrazone was recrystallized from 10 ml. of ethyl alcohol with the aid of Norit; yield 0.075 g. of orange-yellow crystals, m.p. 105–113°; $\lambda_{max(\mu)}^{KBr}$ 5.82 (ester C=O), 6.05 (lactam C=O), 6.66 (NH and NO_2), 7.47 (NO_2), 8.16 (ester C—O—C).

Anal. Calcd. for $C_{23}H_{25}N_5O_7$: C, 57.1; H, 5.21. Found: C, 57.1; H, 5.33.

Methyl 1,2,3,4-tetrahydro-α-methoxy-1,4,4,6,7-pentamethyl-2-oxo-$\Delta^{\alpha,3}$-quinolinacetate (XVII). A stirred mixture of 2.0 g. (9.2 mmoles) of 3,4-dihydro-1,4,4,6,7-pentamethylcarbostyril (XI) and 0.48 g. (0.02 mole) of sodium hydride in 10 g. of dimethyl oxalate and 10 ml. of *N,N*-dimethylformamide was heated at 130–140° for 4.1 hr. The solvents and excess dimethyl oxalate were removed at 60° and 1 mm. pressure. The residue was treated with 25 ml. of ethanol. This mixture was washed with one 50-ml. and one 25-ml. portion of water. The benzene was removed *in vacuo* at 65°, leaving the crude product as tan crystals; weight 2.71 g. Recrystallization of 2.54 g. of the crystals from 35 ml. of ethyl alcohol and 17 ml. of water gave 1.64 g. (60%) of white needles, m.p. 162–166°; $\lambda_{max(\mu)}^{KBr}$ 5.78 (ester C=O), 6.07 (lactam C=O), 6.33 (C=C), 7.65, 8.28 (ester C—O—C), 9.79 (ether C—O—C), 11.28 (1,2,4,5-tetrasubstituted benzene).

Anal. Calcd. for $C_{18}H_{23}NO_4$: C, 68.1; H, 7.31; N, 4.41. Found: C, 68.2; H, 7.18; N, 4.14.

This compound failed to give a 2,4-dinitrophenylhydrazone even when it was refluxed with the reagent for 1 hr.; the enol ether was recovered unchanged.

Sodium 1,2,3,4-tetrahydro-α-methoxy-1,4,4,6,7-pentamethyl-2-oxo-$\Delta^{\alpha,3}$-quinolinacetate (XVIII). To 0.20 g. (0.63 mmole) of recrystallized enol ether (XVII) was added 1 ml. of 1*N* ethanolic sodium hydroxide. After standing overnight, the mixture was heated on the steam bath for 75 min. under reflux. The cooled solution deposited white, flaky crystals. These were collected, washed with 1 ml. of ethyl alcohol, and dried; yield 0.17 g. (83%). The salt did not melt below 295° and had $\lambda_{max(\mu)}^{KBr}$ 6.13 (lactam C=O), 6.25, 7.20 (carboxylate ion), 11.27 (1,2,4,5-tetrasubstituted benzene).

Anal. Calcd. for $C_{17}H_{20}NO_4Na \cdot H_2O$: C, 59.5; H, 6.41. Found: C, 58.9; H, 6.42.

1,2,3,4-Tetrahydro-α-methoxy-1,4,4,6,7-pentamethyl-2-oxo-$\Delta^{\alpha,3}$-quinolinacetic acid (XIX). A suspension of 7.42 g. (0.0226 mole) of the sodium salt (XVIII) in a mixture of 50 ml. of water and 50 ml. of chloroform was acidified with 25 ml. of 6*N* hydrochloric acid, then shaken vigorously. The chloroform layer was separated, dried over magnesium sulfate, and concentrated *in vacuo;* yield 5.91 g. (86.5%), m.p. 168–176°. An analytical sample was prepared by recrystallization from Skellysolve B,[5] then from 25% aqueous methanol, m.p. 175–177°.

Anal. Calcd. for $C_{17}H_{21}NO_4$: C, 67.3; H, 6.98; N, 4.62. Found: C, 67.4; H, 7.12; N, 4.67.

A similar preparation had $\lambda_{max(\mu)}^{KBr}$ 3.8–4.2 (acidic OH), 5.76 (carboxylic acid C=O), 6.10 (lactam C=O), 6.35 (C=C), 9.47 (ether C—O—C), no ester C—O—C at 7.65 or 8.28.

Acid hydrolysis of methyl 1,2,3,4-tetrahydro-α-methoxy-1,4,4,6,7-pentamethyl-2-oxo-$\Delta^{\alpha,3}$-quinolinacetate (XVII). A mixture of 0.06 g. (0.3 mmole) of the recrystallized enol ether (XVII) in 1 ml. of methyl Cellosolve and 2 ml. of 6*N* hydrochloric acid was heated on the steam bath for 1 hr. The solvents were removed *in vacuo*, leaving a colorless oil with $\lambda_{max(\mu)}^{film}$ 5.77 (ester C=O), 6.03 (lactam C=O), 7.81, 8.75 (ester C—O—C), no C=C at 6.33.

The above hydrolysis product was dissolved in 1.5 ml. of methanol and 2.0 ml. of 2,4-dinitrophenylhydrazine reagent. The solution was heated on the steam bath for 1 min. and then cooled in an ice bath. Two drops of water were added. The yellow precipitate that formed was collected by filtration, washed with 1 ml. of 50% methyl alcohol, and dried. The yellow solid melted at 70–85°. The infrared spectrum was similar to that of the 2,4-dinitrophenylhydrazone previously prepared from crude XII; $\lambda_{max(\mu)}^{KBr}$ 5.85 (ester C=O), 6.05 (lactam C=O), 7.50 (NO_2).

1,2,3,4-Tetrahydro-1,4,4,6,7-pentamethyl-2-oxo-3-quinolinecarboxaldehyde (XXV) *2,4-dinitrophenyl hydrazone.* Methyl 1,2,3,4-tetrahydro-α-methoxy-1,4,4,6,7-pentamethyl-2-oxo-$\Delta^{\alpha,3}$-acetate (XIX) (0.512 g., 1.68 mmoles) was heated in a bath at 180–190° for 17.5 min. The solid melted and a gas was evolved. The orange residue weighed 0.427 g. It was dissolved in 7.5 ml. of Skellysolve B[5] and the solution chilled. The yellow crystals that formed were collected on a filter and washed with 2 ml. of Skellysolve B.[5] The crystals weighed 0.210 g., m.p. 135–165°; the infrared spectrum was almost identical with that of methyl 1,2,3,4-tetrahydro-α-methoxy-1,4,4,6,7-pentamethyl-2-oxo-$\Delta^{\alpha,3}$-quinolinacetate (XVII). The filtrate was concentrated *in vacuo*. The orange, viscous residue weighed 0.184 g.; $\lambda_{max(\mu)}^{film}$ 3.71 (aldehyde CH, weak), 5.78 (ester and aldehyde C=O), 5.99 (lactam C=O, 6.22 (>C=C<), 7.43 (CH_3), 11.41 (1,2,4,5-tetrasubstituted benzene).

A solution of 0.163 g. (0.62 mmole) of the above crude aldehyde (XXV) in 2 ml. of ethanol was treated with 10 ml. of 2,4-dinitrophenylhydrazine reagent. Within 1 min. an orange precipitate formed. The mixture was warmed gently on the steam bath for 30 sec., then chilled. The amorphous precipitate was collected, washed with 2 ml. of chilled 60% alcohol, and dried *in vacuo;* yield 0.09 g. (25%, 9% based on XVII), m.p. 135–165°. The infrared spectrum was almost identical with that of a previously prepared analytical sample, m.p. 273–274°; $\lambda_{max(\mu)}^{KBr}$ 3.06 (NH), 6.02 (lactam C=O), 6.11 (aryl + NH + NO_2), 7.54 (NO_2), no ester C=O about 5.8.

Anal. Calcd. for $C_{21}H_{23}N_5O_5$: C, 59.3; H, 5.45. Found: C, 59.3; H, 5.22.

1,4-Dihydro-1,2,4,4,6,7-hexamethylquinoline (XIII). To a stirred solution of 0.01 mole of methyllithium prepared from 0.65 ml. (0.011 mole) of methyl iodide and 0.141 g. (0.021 mole) of lithium metal in 11 ml. of ether was added dropwise with stirring a solution of 1.1 g. (0.0050 mole) of 3,4-dihydro-1,4,4,6,7-pentamethylcarbostyril (XI) in 5 ml. of ether. The resulting solution was stirred for 25 min., then poured onto Dry Ice. After the Dry Ice had evaporated, the mixture was diluted with 60 ml. of ether, then re-extracted with 80 ml. of 0.25*N* sodium hydroxide. After a second extraction with 20 ml. of *N* sodium hydroxide, the ether layer was concentrated to dryness *in vacuo* to give 1.07 g. (99%) of a pink, crystalline solid, m.p. 107–120°. After three recrystallizations from Skellysolve B,[5] white crystals were obtained, m.p. 113.5–114.5°; $\lambda_{max(\mu)}^{KBr}$ 6.00 (C=C—N), 6.20, 6.59, 6.76 (aryl), 7.22 (CH_3), 11.29 (1,2,4,5-tetrasubstituted benzene).

Anal. Calcd. for $C_{15}H_{21}N$: C, 83.7; H, 9.83; N, 6.51. Found: C, 83.2; H, 9.81; N, 6.38.

1,2,3,4-Tetrahydro-1,4,4,6,7-pentamethyl-2-oxo-3-quinolinecarboxylic acid (XV) *and 1,4-dihydro-1,4,4,6,7-pentamethyl-2-quinoline* (XIV). Phenyllithium (0.01 mole) was prepared from 1.57 g. (0.01 mole) of bromobenzene and 0.153 g. (0.022 mole) of lithium metal in 10 ml. of ether in the usual manner. To the stirred phenyllithium solution at room temperature was added 1.62 g. (0.0075 mole) of 3,4-dihydro-1,4,4,6,7-pentamethylcarbostyril (XI) in 10 ml. of ether. The addition was accompanied by an exothermic reaction. The resulting solution was stirred at room temperature for 25 min., then poured onto powdered Dry Ice. After the Dry Ice had evaporated, the resulting mixture was diluted with 45 ml. of ether and extracted with three 35-ml. portions of saturated aqueous sodium bicarbonate solution. The combined alkaline extracts were acidified with dilute sulfuric acid and extracted with 50 ml. of methylene chloride. The methylene chloride was removed *in vacuo* and the brown, viscous residue (0.65 g.) dissolved in hot benzene. The benzene solution was diluted with an equal volume of Skellysolve B,[5] treated with Norit, and filtered. The chilled filtrate yielded 0.46 g. (23.4%) of white crystals of XV, m.p. 146–148° dec. A sample of a pilot preparation formed white crystals, m.p. 145–147° dec.; a 1:1 ratio of phenyllithium to XI was used and the yield was 7.7%; $\lambda_{max(\mu)}^{KBr}$ 3.90 (carboxyl OH), 5.76 (acid C=O), 6.12 (lactam C=O), 7.30 (CH_3, COOH), 11.53 (1,2,4,5-tetrasubstituted benzene).

Anal. Calcd. for $C_{15}H_{19}NO_3$: C, 68.9; H, 7.33. Found: C, 69.1; H, 7.39.

A few milligrams of the recrystallized acid (XV) were heated at 160° until the evolution of gases had ceased (about 4 min.). The infrared spectrum of the solid residue was almost identical with that of an analytical sample of 3,4-dihydro-1,4,4,6,7-pentamethylcarbostyril (XI); $\lambda_{max(\mu)}^{KBr}$ 5.90 (lactam C=O), 11.35 (1,2,4,5-tetrasubstituted benzene).

In a larger run, the ether solution of nonacidic material was dried, then evaporated to dryness *in vacuo;* 1,4-dihydro-1,4,4,6,7-pentamethyl-2-phenylquinoline (XIV) was obtained as a yellow oil, b.p. 158–160° (0.075 mm.); $\lambda_{max(\mu)}^{film}$ 6.02 (C=C–N), 6.18 (aryl), 7.33 (methyl), 11.38 (1,2,4,5-tetrasubstituted benzene).

Anal. Calcd. for $C_{20}H_{23}N$: C, 86.6; H, 8.36; N, 5.05. Found: C, 86.0; H, 8.25; N, 5.06.

Methyl 1,2,3,4-tetrahydro-1,4,4,6,7-pentamethyl-2-oxo-3-quinolinecarboxylate (XVI). (A) A mixture of 5.45 g. (0.021 mole) of 1,2,3,4-tetrahydro-1,4,4,6,7-pentamethyl-2-oxo-3-quinolinecarboxylic acid (XV) and 10 ml. of thionyl chloride was refluxed for 40 min. The resulting solution was evaporated to dryness *in vacuo* and the last traces of thionyl chloride were removed by the addition and removal *in vacuo* of 10 ml. of dry xylene. A solution of the resulting acid chloride in 20 ml. of methanol was refluxed for 30 min., then evaporated to dryness *in vacuo*. The residue was dissolved in 20 ml. of methylene chloride, then washed with 25 ml. of half-saturated aqueous sodium bicarbonate. The organic layer was dried over magnesium sulfate, then evaporated to dryness *in vacuo*. The residue was crystallized from 25 ml. of Skellysolve B[5] to yield 4.86 g. (85%) of crystalline solid, m.p. 110–114°. Recrystallization from Skellysolve B[5] raised the melting point to 115–116.5°; $\lambda_{max(\mu)}^{KBr}$ 5.78 (ester C=O), 6.01 (lactam C=O), 8.64 (ester C—O—C); $\lambda_{max(m\mu)}^{abs.\ alc.}$ 255 (ϵ 9580).

Anal. Calcd. for $C_{16}H_{21}NO_3$: C, 69.8; H, 7.69; N, 5.09. Found: C, 69.8; H, 7.86; N, 4.85.

(B) To a solution of 10.0 g. (0.038 mole) of 1,2,3,4,-tetrahydro-1,4,4,6,7-pentamethyl-2-oxo-3-quinolinecarboxylic acid (XV) in 100 ml. of methanol was added dropwise with swirling 10 ml. of acetyl chloride. The reaction mixture was refluxed for 30 min., then cooled to room temperature. After the addition of a second portion (5 ml.) of acetyl chloride, the reaction mixture was refluxed for 1 hr. more, then concentrated to dryness *in vacuo*. The residue was dissolved in 100 ml. of benzene. The benzene solution was washed with two 75-ml. portions of saturated aqueous sodium bicarbonate and 75 ml. of water, then dried over magnesium sulfate and evaporated to dryness *in vacuo* to yield 9.30 g. of a white, crystalline solid. Recrystallization from 30 ml. of Skellysolve C[5] gave 8.12 g. (77%) of the methyl ester (XVI), m.p. 110–111°, the infrared spectrum of which was essentially identical with that of the analytical sample of procedure A.

1,2,3,4-Tetrahydro-1,4,4,6,7-pentamethyl-2-oxo-3-quinolinecarboxanilide (XX). A solution of 0.26 g. (1.0 mmole) of 1,2,3,4-tetrahydro-1,4,4,6,7-pentamethyl-2-oxo-3-quinoline carboxylic acid (XV) in 3 ml. of thionyl chloride was refluxed for 25 min. The excess thionyl chloride was removed *in vacuo* and the residue was dissolved in 7 ml. of acetone, then 0.25 ml. of aniline was added dropwise with stirring. After 20 min., the reaction mixture was poured in 12 ml. of *N* sulfuric acid and the resulting precipitate was filtered and washed with two 10-ml. portions of sodium carbonate solution to give 0.33 g. (97%) of the anilide (XX), m.p. 232–234°.

An analytical sample was obtained by recrystallization of a similar preparation from aqueous ethanol to give white crystals, m.p. 234–236°; $\lambda_{max(\mu)}^{KBr}$ 3.02 (NH), 6.03 (amide C=O), 6.47 (amide NH), 13.23, 14.42 (phenyl).

Anal. Calcd. for $C_{21}H_{24}N_2O_2$: C, 75.0; H, 7.19. Found: C, 74.6; H, 7.14.

1,2,3,4-Tetrahydro-1,4,4,6,7-pentamethyl-2-oxo-3-quinolinecarboxamide (XXI). A mixture of 1.0 g. (3.65 mmoles) of methyl 1,2,3,4-tetrahydro-1,4,4,6,7-pentamethyl-2-oxo-3-quinolinecarboxylate (XVI) and 1.0 g. of urea was fused at 235–245° for 13 min. After being allowed to cool to room temperature, the residue was powdered, then triturated with water. The water-insoluble material was filtered, then stirred for 30 min. in 10 ml. of concd. hydrochloric acid. A second 10-ml. portion of concd. hydrochloric acid was added and the suspension was stirred an additional 10 min., then filtered. The filtrate was concentrated to dryness *in vacuo* to yield 0.59 g. (54%) of the crude carboxamide (XXI), m.p. 205–225°. Purification was effected by redissolving the solid in 20 ml. of 6*N* hydrochloric acid, decolorizing with Norit, and filtering. The filtrate was diluted with 10 ml. of water, then cooled to 0° and filtered to yield 0.25 g. of the amide (XXI), m.p. 215–220°; $\lambda_{max(\mu)}^{KBr}$ 2.95 (OH, NH), 6.00 (amide C=O).

Anal. Calcd. for $C_{15}H_{20}N_2O_2$: C, 69.2; H, 7.74; N, 10.8. Found: C, 68.9; H, 7.73; N, 10.6.

5,10-Dihydro-2-imino-5,5,7,8,10-pentamethylpyrimido[4,5-b]quinoline-4(4aH)one (XXII). A mixture of 0.95 g. (3.45 mmoles) of methyl 1,2,3,4-tetrahydro-1,4,4,6,7-pentamethyl-2-oxo-3-quinolinecarboxylate (XVI), 0.45 g. (4.75 mmoles) of guanidine hydrochloride, and 0.44 g. (8.15 mmoles) of sodium methoxide in 10 ml. of freshly distilled *N,N*-dimethylformamide was heated at 120° for 5 hr. At the end of this time, the mixture was cooled to 60° and 20 ml. of water was added. The suspended solids all dissolved immediately and a crystalline precipitate of the product (XXII) began to separate. The reaction was cooled to 0°, then filtered to yield 0.58 g. (54%) of a cream-colored solid, m.p. >270°. Recrystallization from 30 ml. of methanol gave 0.42 g. of white needles in two crops. This material was homogeneous on paper chromatography in solvent A,[19] with a blue fluorescent spot at R_f 0.82; $\lambda_{max(m\mu)}^{pH\ 1}$ 326 (ϵ 12,700), $\lambda_{max(m\mu)}^{pH\ 7}$ 321 (ϵ 11,600), $\lambda_{max(m\mu)}^{pH\ 13}$ 307 (ϵ 12,850).

Anal. Calcd. for $C_{16}H_{20}N_4O$: C, 67.6; H, 7.09; N, 19.7. Found: C, 67.7; H, 7.10; N, 20.0.

5,10-Dihydro-5,5,7,8,10-pentamethylpyrimido[4,5-b]quinoline-2,4(3H,4aH)dione (XXIII). To a warm (50–60°) solution of 1.0 g. of XXII in 150 ml. of glacial acetic acid was added dropwise with stirring a solution of 8 g. of sodium nitrite in 20 ml. of water. The solution turned a deep yellow. The reaction mixture was left at room temperature for 4 hr., then a second 8-g. portion of sodium nitrite in 20 ml. of water was added and the solution was stored at room

temperature for 16 hr. The solution was evaporated to dryness *in vacuo* and the residue was washed with several portions of water to remove the inorganic salts, leaving 0.5 g. of insoluble, yellow solid; paper chromatography in solvent A[10] showed two yellow fluorescent spots with R_f values of 0.66 and 0.79, respectively.

Extraction of 148 mg. of this solid with three portions of concd. hydrochloric acid totaling 7 ml. gave 37 mg. of an insoluble material which still contained a mixture of components as shown by paper chromatography. The acid solution was diluted with 42 ml. of water, then cooled to 0° and filtered to yield 68 mg. of yellow solid that was homogeneous on paper chromatography in solvent A with a yellow fluorescent spot at R_f 0.87. A second reprecipitation from 2.5 ml. of concd. hydrochloric acid and 15 ml. of water gave the analytical sample; $\lambda_{max(m\mu)}^{pH\ 1}$ 347 (ϵ 9600), $\lambda_{max(m\mu)}^{pH\ 7}$ 342 (ϵ 10,300), $\lambda_{max(m\mu)}^{pH\ 13}$ 346 (ϵ 8200).

Anal. Calcd. for $C_{16}H_{19}N_3O_2 \cdot HCl$: C, 59.7; H, 6.26; Cl, 11.0; N, 13.1. Found: C, 60.1; H, 5.85; Cl, 10.8; N, 13.2.

3-Chloro-3′,4′-propionoxylidide (XXVI). To a refluxing solution of 80.1 g. (0.667 mole) of 3,4-xylidine (VII) in 70 ml. of acetone was added, with stirring, a solution of 42.6 g. (0.333 mole) of 3-chloropropionyl chloride in 30 ml. of acetone over a period of 50 min. The solution was stirred under reflux for 1 hr. after the addition was completed. The cooled solution was poured into 500 ml. of 1*N* hydrochloric acid. The oil that separated solidified on cooling the mixture in an ice bath. The solid material was dried *in vacuo* overnight at 55° and recrystallized from 280 ml. of 65% aqueous ethanol with use of Norit; yield 61 g. (87%), m.p. 106–109°. A sample recrystallized for analysis formed white crystals, m.p. 109.5°; $\lambda_{max(\mu)}^{KBr}$ 3.03 (NH), 6.04 (amide C=O), 6.46 (amide NH), 12.22 (1,3,4-trisubstituted benzene).

Anal. Calcd. for $C_{11}H_{14}ClNO$: C, 62.4; H, 6.66; Cl, 16.8; N, 6.61. Found: C, 62.7; H, 6.85; Cl, 16.6; N, 6.36.

3,4-Dihydro-6,7-dimethylcarbostyril (XXXII). A mixture of 20 g. (0.104 mole) of 3-chloro-3′,4′-propionoxylidide (XXVI) and 47 g. (0.35 mole) of anhydrous powdered aluminum chloride in 210 ml. of Skellysolve C[5] was heated under reflux with stirring for 2 hr. The stirred mixture was cooled, decomposed with ice, and treated with 30 ml. of 6*N* hydrochloric acid. The white solid was collected on a filter and dried *in vacuo* at 60°; weight 23 g., m.p. 120–150°. The crude product was recrystallized from 65 ml. of ethanol with the use of Norit; yield 7.1 g., m.p. 180–195°. The product was purified further by recrystallization from methanol-ethanol (95 ml.: 15 ml.); yield of pure product, 5.0 g. (30%). The colorless flat needles melted at 199–202°; $\lambda_{max(\mu)}^{KBr}$ 3.12 (NH), 5.96 (lactam C=O), 7.25 (methyl); 11.28 (1,2,4,5-tetrasubstituted benzene). The infrared spectrum was identical with that of an analytical sample which had been prepared in 12% yield by the fusion of aluminum chloride with 3-chloro-3′,4′-propionoxylidide (XXVI).

Anal. Calcd. for $C_{11}H_{13}NO$: C, 75.4; H, 7.48; N, 7.99. Found: C, 75.3; H, 7.71; N, 7.76.

3,4-Dihydro-1,6,7-trimethylcarbostyril (XXXIII). A stirred mixture of 8.9 g. (0.051 mole) of 3,4-dihydro-6,7-dimethylcarbostyril (XXXII) and 1.30 g. (0.054 mole) of sodium hydride in 75 ml. of *N,N*-dimethylformamide was warmed gently on the steam bath until most of the sodium hydride had reacted. The mixture was stirred with ice cooling while 3.7 ml. (8.5 g., 0.060 mole) of methyl iodide was added. Stirring was maintained with ice cooling for 15 min. and then the mixture was warmed on the steam bath with occasional stirring for 15 min. more. The solvent was removed *in vacuo* and the residue suspended in 75 ml. of chloroform. The suspension was washed with two 125-ml. portions of water. The chloroform solution, dried over magnesium sulfate, was concentrated *in vacuo*. The residue (8.0 g.) was distilled, b.p. 109° (0.06 mm.) (bath temperature 120–130°); weight 7.55 g. The oil was dissolved in 25 ml. of Skellysolve B[5] and the solution chilled to yield 7.50 g. (77.8%) of white crystals, m.p. 46.5–48.0°. A recrystallized sample melted at 47.5–49.5°; $\lambda_{max(\mu)}^{KBr}$ 5.95 (lactam C=O), 11.30 (1,2,4,5-tetrasubstituted benzene).

Anal. Calcd. for $C_{12}H_{15}NO$: C, 76.2; H, 7.99. Found: C, 76.3; H, 8.01.

1-(3,4-Xylyl)-2-azetidinone (XXX). A stirred solution of 8.64 g. (0.041 mole) of 3-chloro-3′,4′-propionoxylidide (XXVI) in 75 ml. of *N,N*-dimethylformamide was treated with 1.1 g. (0.046 mole) of sodium hydride. Hydrogen was evolved and the temperature of the reaction mixture rose to 35°. After 5 min. the vigorous reaction had subsided and the milky suspension was stirred 5 min. at 20°, then 5 min. on the steam bath. The solvent was removed *in vacuo* and the residue was dissolved in 50 ml. of benzene. The benzene solution was washed with two 50-ml. portions of water, dried over magnesium sulfate, and concentrated *in vacuo*. The residue (5.45 g.) distilled at 103–110° (0.15 mm.) (bath temperature 135–180°). The distillate (1.45 g.) was dissolved in 21 ml. of Skellysolve B[5]–benzene (20:1) and chilled. The white crystals were collected; yield 0.52 g. (7.2%), m.p. 101–103°. Recrystallization from benzene–Skellysolve B raised the m.p. to 104–105°; $\lambda_{max(\mu)}^{KBr}$ 5.76 (β-lactam C=O), 6.65 (aryl), 7.21 (CH_3), 12.35 (1,2,4-trisubstituted benzene), no amide NH at 3.03 or 6.48.

Anal. Calcd. for $C_{11}H_{13}NO$: C, 75.4; H, 7.48. Found: C, 75.4; H, 7.57.

3-Chloro-N-methyl-3′,4′-propionoxylidide (XXIX). To a stirred solution of 5.0 g. (0.024 mole) of 3-chloro-3′,4′-propionoxylidide (XXVI) and 5.76 g. (0.30 mole) of methyl iodide in 25 ml. of *N,N*-dimethylformamide was added 0.65 g. (0.027 mole) of sodium hydride. Vigorous evolution of hydrogen occurred and the temperature rose to 50°. The mixture was chilled in an ice bath to 20° and an additional 2.28 g. of methyl iodide was added. The stirring with ice-cooling was continued for 15 min. The reaction mixture was poured into 350 ml. of ice water and the aqueous mixture was extracted with two 45-ml. portions of methylene chloride. Concentration of the combined extracts *in vacuo* yielded 3.55 g. of a viscous liquid that distilled at 96–100° (0.05 mm.) (bath temperature 120–130°); weight 1.84 g. From its infrared spectrum the mixture was judged to be about a 2:1 mixture of the expected product (XXIX) and β-lactam (XXX); $\lambda_{max(\mu)}^{film}$ 5.73 (β-lactam C=O), 6.04 (amide C=O), 12.13 (1,2,4-trisubstituted benzene), no NH about 3.0.

Methyl 1,2,3,4-tetrahydro-1,6,7-trimethyl-2-oxo-3-quinolineglyoxylate (XXXVIII) *2,4-dinitrophenylhydrazone*. A stirred mixture of 2.0 g. (0.011 mole) of 3,4-dihydro-1,6,7-trimethylcarbostyril (XXXIII) and 0.54 g. (0.023 mole) of sodium hydride in 7.5 g. of dimethyl oxalate and 7.6 ml. of *N,N*-dimethylformamide was heated under reflux for 2.5 hr. The solvent was removed *in vacuo* and the residue was suspended in 35 ml. of benzene. The excess sodium hydride was decomposed with 3 ml. of acetic acid. The resulting suspension was washed with 30 ml. of half-saturated sodium bicarbonate solution. The bicarbonate wash was extracted with 35 ml. of chloroform. The combined organic solutions were washed with 50 ml. of water, dried over magnesium sulfate, and concentrated *in vacuo*, finally at 80° (0.05 mm.). A brown, viscous residue was obtained; weight 2.40 g.; $\lambda_{max(\mu)}^{film}$ 5.75 (ester C=O), 6.00 (shoulder, ketone C=O), 6.06 (lactam C=O), 7.91 (ester C—O—C), no enol ether C=C at 6.3.

To a solution of 0.645 g. (2.34 mmoles) of the crude methyl 1,2,3,4-tetrahydro-1,6,7-trimethyl-2-oxo-3- quinolineglyoxylate (XXXVIII) was added 18 ml. of freshly prepared methanolic 2,4-dinitrophenylhydrazine reagent containing 0.54 g. (2.7 mmoles) of the hydrazine. After several seconds, an orange precipitate formed and the mixture was heated to boiling on the steam bath and then chilled. The precipitate was collected on a filter and washed with 3 ml. of cold methanol. The moist precipitate was suspended in 25 ml. of water and the acid solution was neutralized with saturated sodium bicarbonate solution. The amorphous solid was collected on a filter and dried *in vacuo;* yield 0.22 g. (21%), m.p. about 120–140°. Recrystallization from a mixture of

methanol, ethanol, and ethyl acetate yielded a crystalline sample which melted at 252–255° and which was not quite pure; $\lambda_{max(\mu)}^{KBr}$ 3.02 (shoulder, NH), 5.78 (ester C=O), 6.02 (lactam C=O), 6.19 (aryl + C=N), 6.65 (aryl + NH + NO_2), 6.93 (NO_2), 11.51 (1,2,4,5-tetrasubstituted benzene).

Anal. Calcd. for $C_{21}H_{21}N_5O_7$: C, 55.4; H, 4.65; N, 15.4. Found: C, 54.8; H, 4.74; N, 14.6.

Ethyl 1,2,3,4-tetrahydro-1,6,7-trimethyl-2-oxo-3-quinolinecarboxylate (XXXV). A stirred mixture of 5.0 g. (0.026 mole) of 3,4-dihydro-1,6,7-trimethylcarbostyril (XXXIII) and 1.3 g. (0.054 mole) of sodium hydride in 12.5 ml. of ethyl carbonate and 12.5 ml. of *N,N*-dimethylformamide was refluxed for 1.1 hr. The volatile materials were removed *in vacuo* and the residue was dissolved in 100 ml. of benzene. The benzene solution was washed with 50 ml. of water, dried over magnesium sulfate, then concentrated *in vacuo*. The residue (4.88 g.) was dissolved in a solution of 14 ml. of benzene and 21 ml. of Skellysolve B,[5] then chilled. The crystalline material was collected and washed with 10 ml. of Skellysolve B[5]; yield 1.98 g., m.p. 90–95°. A second crop weighing 0.90 g., m.p. 85–95°, was obtained. The combined yield was 2.88 g. (42%). An analytical sample was prepared from a similar run by several recrystallizations from benzene–Skellysolve B,[5] m.p. 98–100°; $\lambda_{max(\mu)}^{KBr}$ 5.78 (ester C=O), 6.00 (lactam C=O), 8.41 (ester C—O—C); $\lambda_{max(m\mu)}^{pH\ 1,7,13}$ 258 (ϵ 10,400).

Anal. Calcd. for $C_{15}H_{19}NO_3$: C, 68.9; H, 7.33. Found: C, 69.1; H, 7.41.

1,2,3,4-Tetrahydro-1,6,7-trimethyl-2-oxo-3-quinolinecarboxylic acid (XXXVII). A solution of 0.60 g. (2.3 mmoles) of ethyl 1,2,3,4-tetrahydro-1,6,7-trimethyl-2-oxo-3-quinolinecarboxylate (XXXV) in 6 ml. of 1.25*N* sodium hydroxide solution was refluxed on the steam bath for 1 hr., the resulting solution was chilled, and the white, crystalline sodium salt (XXXVI) was collected; yield 0.46 g. (79%), m.p. 160–165°; $\lambda_{max(\mu)}^{KBr}$ 6.04 (lactam C=O), 6.20, 7.00 (carboxylate).

To a suspension of 0.40 g. (1.58 mmoles) of the sodium salt (XXXVI) in 7.5 ml. of water, 5 g. of methylene chloride, and 5 ml. of chloroform was added 2 ml. of 6*N* hydrochloric acid. The mixture was shaken, then the organic layer was separated and concentrated to dryness *in vacuo* to give 0.28 g. (80%) of a white, crystalline solid, m.p. 160–161° dec. (rapid heating). Recrystallization from benzene–Skellysolve B[5] gave white crystals, m.p. 154.5–155.5°, $\lambda_{max(\mu)}^{Nujol}$ 5.77 (acid C=O), 6.08 (lactam C=O).

Anal. Calcd. for $C_{13}H_{15}NO_3$: C, 66.9; H, 6.48; N, 6.01. Found: C, 66.9; H, 6.37; N, 6.03.

Pyrolysis of this acid (XXXVII) at 180° caused a vigorous evolution of gas. After 3.5 min., gas evolution ceased and the infrared spectrum of the resulting product was identical with that of 3,4-dihydro-1,6,7-trimethylcarbostyril (XXXIII); $\lambda_{max(\mu)}^{film}$ 5.97 (lactam C=O), 7.42 (CH_3), 11.35 (1,2,4,5-tetrasubstituted benzene).

1,2,3,4-Tetrahydro-1,6,7-trimethyl-2-oxo-3-quinolinecarboxylic acid hydrazide (XXXIV). A solution of 0.50 g. (1.92 mmoles) of ethyl 1,2,3,4-tetrahydro-1,6,7-trimethyl-2-oxo-3-quinolinecarboxylate (XXXV) in 5 ml. of hydrazine hydrate and 5 ml. of ethanol was heated on a steam bath for 30 min., then poured into 100 ml. of water and kept at 0° overnight. The white, flocculent precipitate was collected, washed with water, and dried *in vacuo;* yield 0.42 g. (91.5%), m.p. 182.5–183.5°; $\lambda_{max(\mu)}^{KBr}$ 3.02 (OH, NH), 6.00 (C=O and C=N), 7.39 (CH_3), 11.40 (1,2,4,5-tetrasubstituted benzene); $\lambda_{max(m\mu)}^{pH\ 1}$ 257 (ϵ 10,350), $\lambda_{max(m\mu)}^{pH\ 7}$ 256 (ϵ 10,550), $\lambda_{max(m\mu)}^{pH\ 13}$ 254 (ϵ 12,620).

An analytical sample was recrystallized from benzene, m.p. 178–180°.

Anal. Calcd. for $C_{13}H_{17}N_3O_2$: C, 63.1; H, 6.93; N, 17.0. Found: C, 63.5; H, 7.21; N, 16.9.

Ethyl 3-bromo-1,2,3,4-tetrahydro-1,6,7-trimethyl-2-oxo-3-quinolinecarboxylate (XLIV) *and 'dibromide'* (XLIII). To a stirred solution of 2.61 g. (0.01 mole) of ethyl 1,2,3,4-tetrahydro-1,6,7-trimethyl-2-oxo-3-quinolinecarboxylate (XXXV) in 20 ml. of chloroform was added dropwise 0.55 ml. (0.011 mole) of bromine. After an initial induction period of a few minutes, the bromine color was discharged almost immediately after each drop was added. After the addition was complete, the orange solution was stirred for 5 min., then the solvent was removed *in vacuo* with a bath temperature of 30°. Trituration of the resulting yellow oil with 40 ml. of benzene–Skellysolve B[5] (1:1) caused crystallization of the 'dibromide' (XLIII) to occur. The orange-yellow crystals were removed by filtration to yield 1.20 g., m.p. 90°, resolidifying at 110–120° and remelting at 245–248° (the melting point of XLVIII).

The filtrate was cooled at 0° overnight, then filtered to yield 0.78 g. (23%) of almost white monobromide (XLIV), m.p. 120–125°, resolidifying at 130–135° and remelting at 230–240°; $\lambda_{max(\mu)}^{KBr}$ 5.70 (ester C=O), 6.03 (lactam C=O, 8.03 8.12 (ester C—O—C), 11.26 (1,2,4,5-tetrasubstituted benzene).

Anal. Calcd. for $C_{15}H_{18}BrNO_3$: C, 53.0; H, 5.33; Br, 23.5. Found: C, 53.3; H, 5.53; Br, 20.0. A satisfactory bromine analysis could not be obtained.

From a similar run, 1.00 g. of the dihydro ester (XXXV) and 0.20 ml. of bromine gave 0.55 g. of the 'dibromide' (XLIII), m.p. 90–91°, resolidifying at 125–130° and remelting at 246–248°; $\lambda_{max(\mu)}^{KBr}$ 5.78, 5.83 (ester C=O), 6.13 (lactam C=O).

Anal. Calcd. for dibromide of XXXV: Br, 38.2. Found: Br, 37.8.

A solution of 102 mg. of the 'dibromide' (XLIII) in 5 ml. of chloroform was extracted with two 5-ml. portions of saturated aqueous sodium bicarbonate and 5 ml. of water. The aqueous layers were back-extracted with 5 ml. of chloroform. The chloroform layers were combined and dried over magnesium sulfate, then evaporated to dryness *in vacuo* to yield 53 mg. of a yellow oil which crystallized on standing. The infrared spectrum of this material was identical with that of authentic ethyl 1,2-dihydro-1,6,7-trimethyl-2-oxo-3-quinolinecarboxylate (XLVII).

Treatment of 101 mg. of the monobromide (XLIV) with saturated aqueous sodium bicarbonate under the same conditions gave a quantitative recovery of the starting monobromide (XLIV).

1,2-Dihydro-1,6,7-trimethyl-2-oxo-3-quinolinecarboxylic acid (XLVIII). A flask containing 0.348 g. (1 mmole) of ethyl 3-bromo-1,2,3,4-tetrahydro-1,6,7-trimethyl-2-oxo-3-quinolinecarboxylate (XLIV) was heated at 160° for 5 min. The bromoester melted and evolved a gas, then the melt resolidified. The cream-colored crystalline residue weighed 0.228 g. (98.6% yield), m.p. 235–250°. The crude acid (XLIII) was dissolved in 10 ml. of 1*N* aqueous sodium hydroxide, then was washed with 10 ml. of chloroform. The aqueous layer was diluted with 10 ml. of water, then neutralized with 6*N* sulfuric acid. The cream-colored precipitate was filtered, washed with water, then dried to yield 0.224 g. (97%) of the carboxylic acid (XLVIII), m.p. 250–253°; $\lambda_{max(\mu)}^{KBr}$ 5.80 (acid C=O), 6.17 (lactam C=O, C=C), 11.44 (1,2,4,5-tetrasubstituted benzene); $\lambda_{max(m\mu)}^{pH\ 1}$ 364 (ϵ 8200), $\lambda_{max(m\mu)}^{pH\ 7}$ 353 (ϵ 8450), $\lambda_{max(m\mu)}^{pH\ 13}$ 341 (ϵ 7900.

Anal. Calcd. for $C_{13}H_{13}NO_3$: C, 67.5; H, 5.67; N, 6.06. Found: C, 67.3; H, 5.74; N, 5.97.

Methyl 1,2-dihydro-1,6,7-trimethyl-2-oxo-3-quinolinecarboxylate (XLVI). A solution of 2.0 g. (8.65 mmoles) of 1,2-dihydro-1,6,7-trimethyl-2-oxo-3-quinolinecarboxylic acid (XLVIII) in 16 ml. of thionyl chloride was refluxed for 1 hr. The reaction was evaporated to dryness *in vacuo* and the last traces of thionyl chloride were removed by the addition and evaporation *in vacuo* of 10 ml. of dry benzene; $\lambda_{max(\mu)}^{Nujol}$ 5.65 (acid chloride C=O).

The yellow, crystalline solid was dissolved in 25 ml. of benzene-methanol (1:1), then refluxed for 10 min. and left at room temperature overnight. Removal of the solvent *in vacuo* gave a crystalline residue which was dissolved in methylene chloride and washed with 10 ml. of saturated aqueous sodium bicarbonate. Evaporation of the methylene

chloride *in vacuo* followed by recrystallization of the residue from benzene gave 1.56 g. (74%) of the carbomethoxy derivative (XLVI), m.p. 153–157°, in two crops; $\lambda_{max(\mu)}^{KBr}$ 5.76 (ester C=O), 6.11 (lactam C=O and aryl), 6.22 (C=C), 11.32 (1,2,4,5-tetrasubstituted benzene).

Anal. Calcd. for $C_{14}H_{18}NO_3$: C, 68.6; H, 6.16; N, 5.71. Found: C, 68.6; H, 6.21; N, 5.64.

Ethyl 1,2-dihydro-1,6,7-trimethyl-2-oxo-3-quinolinecarboxylate (XLVII) was prepared in 78% yield, m.p. 105,–109°, by the procedure described for the carbomethoxy derivative (XLVI).

Recrystallization from benzene–Skellysolve B[5] raised the melting point to 109–110°; $\lambda_{max(\mu)}^{KBr}$ 5.78 (ester C=O), 5.90, 6.07 (lactam C=O); $\lambda_{max(m\mu)}^{pH\ 1}$ 359 (ε 7400), $\lambda_{max(m\mu)}^{pH\ 7}$ 362 (ε 7400), $\lambda_{max(m\mu)}^{pH\ 13}$ 338 (ε 8200).

Anal. Calcd. for $C_{15}H_{17}NO_3$: C, 69.5; H, 6.61; N, 5.40. Found: C, 69.2; H, 6.70; N, 5.24.

1,2-Dihydro-1,6,7-trimethyl-2-oxo-3-quinolinecarboxylic acid, hydrazide (XLV). A solution of 0.117 g. (4.5 mmoles) of ethyl 1,2-dihydro-1,6,7-trimethyl-2-oxo-3-quinolinecarboxylate (XLVII) in 1.2 ml. of methanol was treated with 0.5 ml. of hydrazine hydrate. After about 3 min., a crystalline precipitate separated. The resulting mixture was heated on a steam bath for 1 min., then diluted with 10 ml. of water. The crystalline precipitate was filtered, then dried to yield 0.105 g. (95%), m.p. 215.0–215.5°; $\lambda_{max(\mu)}^{KBr}$ 3.07 (NH), 6.02 (C=O); $\lambda_{max(m\mu)}^{pH\ 1}$ 365 (ε 7370), $\lambda_{max(m\mu)}^{pH\ 7}$ 360 (ε 8800), $\lambda_{max(m\mu)}^{pH\ 13}$ 354 (ε 7860).

Anal. Calcd. for $C_{15}H_{15}N_3O_2$: C, 63.6; H, 6.16; N, 17.1. Found: C, 63.7; H, 6.32; N, 17.0.

2,10-Dihydro-2-imino-7,8,10-trimethylpyrimido[4,5-b]-quinoline-4(3H)one (L) *acetate.* A mixture of 290 mg. (3.06 mmoles) of guanidine hydrochloride, 500 mg. (2.04 mmoles) of methyl 1,2-dihydro-1,6,7-trimethyl-2-oxo-3-quinolinecarboxylate (XLVI), and 6 ml. of 1*N* methanolic sodium methoxide was refluxed for 3 hr., then cooled and diluted with 25 ml. of water and 5 ml. of saturated aqueous sodium bicarbonate. The precipitate was filtered and washed with water, then dried to give 230 mg. of crude L as a yellow solid.

The acetate salt of L was prepared by heating 50 mg. of the above yellow solid in 30 ml. of 85% acetic acid on a steam bath for 30 min. After being allowed to cool, the supernatent liquid was separated by centrifugation and the solid was dried; yield 48 mg. of yellow solid, m.p. >300°, which was homogeneous on paper chromatography in solvent B[10] with R_f 0.57.

Anal. Calcd. for $C_{14}H_{14}N_4O \cdot HC_2H_3O_2$: C, 61.1; H, 5.77; N, 17.8. Found: C, 61.0; H, 5.62; N, 17.5.

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Synthesis and Reactions of Monosubstituted Triptych-Boroxazolidines[1]

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The synthesis of a series of 3-alkyl, 3-aryl, 3-alkoxymethyl, and 3-dialkylaminomethyltriptych-boroxazolidines has been carried out. In addition, several triptychboroxazolidines carrying reactive functional groups at the 3-position have been prepared including the 3-chloromethyl, 3-hydroxymethyl, 3-aminomethyl, and 3-cyanomethyl compounds. Certain of the reactions of the 3-chloromethyl and 3-aminomethyltriptych-boroxazolidines have been investigated with particular reference to the linking of an amino acid moiety to the triptych-boroxazolidine moiety. Although the chloromethyl compound proved to be of limited use in this respect, the aminomethyl compound has provided a boron-containing amino acid, a compound of possible interest in cancer chemotherapy.

The suggestion by Kruger that the neutron-induced disintegration of boron should be applicable to cancer chemotherapy[3] and the demonstration by Christensen *et al.*[4] that some of the amino acids selectively concentrate in certain tumor cells provided the incentive to investigate the synthesis of boron-containing amino acids.[5] The present work involves certain aspects of the chemistry of the triptych-boroxazolidine type of compound[6] and had as its aim the incorporation of this moiety in an amino acid. Triethanolamine borate (I), the simplest triptych-boroxazolidine, was reported first in 1933 in a German patent[7] and investigated in much more detail by Brown and Fletcher[8] and by Hein and Burckhardt.[9] It is with monosubstituted triethanolamine borates that the present paper is concerned, although from the standpoint of a therapeutic agent the triethanolamine borate ring is not the most desirable,

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(2) Postdoctoral Research Associate 1958–1959.

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