fied by passing it through a tower containing potassium hydroxide and calcium chloride, was bubbled through the solution for 2 hr. Next, 0.25 mole of alkyl Grignard was added, and the temperature was allowed to rise to 0° with continued stirring and oxidation for 2 hr. Then the remaining 0.25 mole of alkyl Grignard reagent was added, and stirring and oxidation were continued for 1 hr. in an ice bath. The solution was then stirred and oxidized for 2 hr. at room temperature. After the salts had been dissolved with dilute hydrochloric acid, the solution was extracted with ether. After drying over anhydrous sodium sulfate, the ether was removed under vacuum. Thirty grams of 2-hydroxythianaphthene distilled at 60–90°/0.1 mm. Recrystallization from petroleum ether (b.p. 00–00°) low boiling gave the keto form, m.p. 32–35°, 40%.

N-o-Mercaptophenyl-N-phenylacetamide. The addition of 2-hydroxythianaphthene to aniline resulted in an instantaneous formation of the amide, which after recrystallization from ethylene glycol dimethyl ether, melted at 212.5°.

Anal. Calcd. for $C_{14}H_{13}NOS$: C, 69.11; H, 5.38; N, 5.76; S, 13.18. Found: C, 69.04; H, 5.14; N, 5.99; S, 13.18.

2-Thianaphthenylphenylamine. Five grams of 2-hydroxythianaphthene was added to 12.5 g. of aniline. Three drops of hydrochloric acid was added as a catalyst. The reaction mixture was refluxed for 24 hr. Upon vacuum distillation a compound melting at 117–118° was obtained. Both analysis and the infrared spectrum substantiate the amine structure.

Anal. Calcd. for $C_{14}H_{11}NS$: C, 74.63; H, 4.96; N, 622; S, 14.23; Found: C, 74.49; H, 4.70; N, 6.28; S, 14.49.

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HOLLAND, MICH.

[CONTRIBUTION FROM THE CHEMISTRY LABORATORY, DEPAUW UNIVERSITY]

Bromination Studies of Alkyl-Substituted 2-Pyridones and 2-Quinolones[1]

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A number of brominated 2-pyridines and 2-quinolones have been prepared and identified. The usefulness of *N*-bromosuccinimide for side chain bromination on *N*-methyl-3- and 5-methyl-2-pyridones has been demonstrated as well as the bromination of side chains in the homocyclic ring of the 2-quinolones. If the active 3- position of the carbostyrils is substituted by a methyl group, *N*-bromosuccinimide will introduce a bromine atom into this group. If the 3- position is open and no methyl groups appear in the homocyclic ring of the carbostyril, the ring is brominated in the 3- position. Some evidence is given which indicates that *N*-bromosuccinimide bromination proceeds by two different mechanisms. The action of *N*-bromosuccinimide on the substituted carbostyrils appears to be similar to the action of *N*-bromosuccinimide on coumarins.

Since the early 1940's the Wohl-Ziegler reaction has been extended to include a large number of allylic systems. The purpose of this work was to undertake a study of how *N*-bromosuccinimide acts upon the methyl-substituted 2-pyridones and 2-quinolones. The latter compounds are commonly called carbostyrils.

Adams and Schrecker[3] have used *N*-bromosuccinimide in an attempt to prepare 6-bromomethyl-2-pyridone from 6-methyl-2-pyridone. They obtained 3,5-dibromo-6-methyl-2-pyridone. Similar results were obtained by Mariella and Belcher[4] when they treated 4,6-dimethyl-2-pyridone with *N*-bromosuccinimide and obtained 3,5-dibromo-4,6-dimethyl-2-pyridone. Under drastic free radical conditions with *N*-bromosuccinimide the compound 3,5-dibromo-4,6-dibromomethyl-2-pyridone was obtained. Although elementary bromine has been used to brominate 1,4-dimethylcarbostyril[5] and 4-methylcarbostyril[6] to produce a 3-bromo-substituted carbostyril in each case, *N*-bromosuccinimide has not been previously used as a reagent for the bromination of methyl-substituted carbostyrils.

Hasegawa[7] has been able to prepare 4-bromomethylcarbostyril by the bromination of acetoacetanilide with bromine in chloroform and subsequent ring closure of the ω-bromoacetoacetanilide to the brominated carbostyril.

Since the use of *N*-bromosuccinimide on 2-pyridones easily substituted the 3- and 5-ring positions with bromine,[3,4] it was of interest to see the results of *N*-bromosuccinimide with benzoyl peroxide as a catalyst on 3-methyl-, 5-methyl-, 1,3-dimethyl-, and 1,5-dimethyl-2-pyridone. In the reaction of the dimethyl-2-pyridones, reactive monobromo derivatives were obtained which are believed to be 3-bromomethyl-1-methyl-2-pyridone (I) and 5-bromomethyl-1-methyl-2-pyridone (II), respectively. The monomethyl 2-pyridones gave oils which decomposed upon distillation.

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(2) Portions of this article are taken from the theses of R.E.B. (1960) and P.S. (1958) which were presented to the Chemistry Department of DePauw University in partial fulfillment of the M.A. degrees.

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(4) R. P. Mariella and E. P. Belcher, *J. Am. Chem. Soc.*, **74**, 1916 (1952).

(5) L. Knorr, *Ann.*, **236**, 91 (1886).

(6) M. Chick and N. T. M. Wilsmore, *J. Chem. Soc.*, **97**, 1981 (1910).

(7) M. Hasegawa, *Pharm. Bull.*, **1**, 50 (1953); *Chem. Abstr.*, **49**, 12470 (1955).

When 1,4- and 1,6-dimethyl-2-pyridone were treated with one equivalent of *N*-bromosuccinimide and peroxide, mixtures were obtained. When two equivalents of *N*-bromosuccinimide were used, the unreactive dibromo derivatives were obtained and were assigned the structures of 3,5-dibromo-1,4-dimethyl-2-pyridone (III) and 3,5-dibromo-1,6-dimethyl-2-pyridone (IV), respectively. Evidence that IV had been formed was obtained by converting the known 3,5-dibromo-6-methyl-2-pyridone to its *N*-methyl derivative and showing it to be identical to IV. 4-Methyl-2-pyridone, when treated with two equivalents of *N*-bromosuccinimide gave the unreactive dibromo derivative that has been assigned the structure of 3,5-dibromo-4-methyl-2-pyridone (V).

An attempt to brominate 1-methyl-2-pyridone with *N*-bromosuccinimide in the presence of benzoyl peroxide gave no product, but when two equivalents of *N*-bromosuccinimide were employed in the presence of aluminum chloride, 3,5-dibromo-1-methyl-2-pyridone (VI)[8] was obtained.

The failure of *N*-bromosuccinimide to brominate the methyl groups of many of the 2-pyridones can be attributed to the presence of the lactam group since Buu-Hoi[9] reported that 2- and 4-methylpyridines give side chain bromination. However, when the 3- or 5-position in the 2-pyridones are substituted with methyl groups, *N*-bromosuccinimide does give side chain bromination on these groups. The only contribution that the *N*-methyl group appears to make to the success of the reaction is the relative ease of purification of the products. Bromination of 2-pyridones with bromine in acetic acid gives 3,5-dibromo products when these positions are not substituted. Bromination of 3-methyl-2 pyridone with bromine in acetic acid gave an unreactive monobromo derivative which was assigned the structure of 5-bromo-3-methyl-2-pyridone (VII).

In a manner somewhat analogous to the pyridones, a study of the action of *N*-bromosuccinimide in the presence of benzoyl peroxide on various carbostyrils was undertaken. Treatment of 4-methyl- and 1,4-dimethylcarbostyril with *N*-bromosuccinimide and the peroxide gave 3-bromo-4-methylcarbostyril (VIII) and 3-bromo-1,4-dimethylcarbostyril (IX), respectively. Both VIII and IX are known.[5,6] 4-Bromomethyl-1-methylcarbostyril (X) was prepared by a known method.[6] Further evidence that this was X was obtained by converting the known 4-hydroxymethyl-1-methylcarbostyril to the bromo derivative with phosphorous tribromide. The products by the two methods were identical. Compounds VIII and IX gave no infrared absorption band in the 900 to 860-cm.$^{-1}$ region, whereas X and the known 4-bromomethylcarbostyril (XI)[6] gave absorptions at 904 and 868 cm.$^{-1}$, respectively, which is indicative of the single hydrogen in the 3-position. These observations show that *N*-bromosuccinimide does not give allylic bromination in the 4-methyl group of 4-methyl- and 1,4-dimethylcarbostyril. Once the 3-position was brominated, it was possible to convert IX to 4-bromomethyl-3-bromo-1-methylcarbostyril (XII) with *N*-bromosuccinimide and the peroxide.

As the pyridones were brominated on the side chain whenever a methyl group was substituted on the 3-ring position, it was of interest to prepare 3,4-dimethyl- and 1,3,4-trimethylcarbostyril and treat them with *N*-bromosuccinimide in the presence of the peroxide. In both cases reactive monobromo derivatives were obtained. Evidence that 3,4-dimethylcarbostyril had been converted to 3-bromomethyl-4-methylcarbostriyl (XIII) was obtained by converting the silver salt of 3-(4-methylcarbostyril)acetic acid to XIII by the Hunsdiecker reaction. The two compounds were identical. When 1,3,4-trimethylcarbostyril was treated with *N*-bromosuccinimide in a similar manner, 3-bromomethyl - 1,4 - dimethylcarbostyril was obtained (XIV). The other possible compound, 4-bromomethyl-1,3-dimethylcarbostyril (XV) was prepared by direct bromination of α-methyl-*N*-methylacetoacetanilide followed by ring closure to give the product.

To further study the action of *N*-bromosuccinimide on substituted carbostyrils, 4,8-dimethylcarbostyril was brominated in the presence of benzoyl peroxide to give a reactive monobromo compound which was converted to the acetoxy derivative and subsequently to the alcohol. Proof that this compound was 8-bromomethyl-4-methylcarbostyril (XVI) was made by preparing 4-bromomethyl-8-methylcarbostyril (XVII) by direct bromination of acetoacet-*o*-toluidide and converting to XVII by ring closure. Compounds XVI and XVII had dissimilar infrared spectra. Bromination of 4,8-dimethylcarbostyril with *N*-bromosuccinimide in the presence of aluminum chloride gave an unreactive monobromo derivative that would not give an acetoxy derivative. Infrared analysis of this compound showed no absorption in the 900- to 860-cm.$^{-1}$ region. On the basis of this evidence the compound was assigned the structure of 3-bromo-4,8-dimethylcarbostyril (XVIII). When the bromination was repeated using bromine in acetic acid, XVIII was also isolated. The fact that 4,8-dimethylcarbostyril when brominated with *N*-bromosuccinimide under conditions known to favor free radical reactions gave side chain bromination while when brominated with *N*-bromosuccinimide under conditions thought to favor ionic reactions (aluminum chloride) gave ring substitution was considered strong evidence that the reaction of *N*-bromosuccinimide can proceed by two different mechanisms. These observations agree with those

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(9) N. P. Buu-Hoi, *Ann.*, **556**, 1 (1944).

of Ross, Finkelstein, and R. C. Petersen[10] who studied the action of *N*-bromosuccinimide on toluene in the presence of benzoyl peroxide and chloranil. As further evidence that side chain bromination can take place when a methyl group appears in the homocyclic ring of the carbostyrils, 1,4,7-trimethylcarbostyril, when treated with *N*-bromosuccinimide in the presence of the peroxide, gave a reactive monobromo derivative. In accord with the previous observations of the unreactivity of the 4-methyl group to *N*-bromosuccinimide and the reactivity of the homocyclic methyl groups, this compound was assigned the structure of 7-bromomethyl-1,4-dimethylcarbostyril (XIX).

In much of the study with *N*-bromosuccinimide on the carbostyrils the similarity to the coumarins has been observed. Since it is known that the action of bromine on coumarin yields a 3,4- addition compound,[11] it was of interest to find if the carbostyrils had the same property. The treatment of 1,4-dimethyl- and 1-methylcarbostyril in chloroform with bromine gave 3,4-dibromodihydro-1,4-dimethylcarbostyril (XX) and 3,4-dibromodihydro-1-methylcarbostyril (XXI), respectively. XX was stable in a dry atmosphere but when heated with water, it was converted to IX. XXI was converted to the known 3-bromo-1-methylcarbostyril by hydrolysis.

DISCUSSION

The preceding evidence indicates that *N*-bromosuccinimide can dissociate by either a homolytic or a heterolytic mechanism. So far all attempts to introduce a bromine into the methyl group on the 4-position of the carbostyrils or the 4- or 6-position of the 2-pyridones have failed. Molho and Mentzer[12] noted the same unreactivity of the 4-methyl group in the attempted bromination of 7-methoxy-4-methylcoumarin with *N*-bromosuccinimide. From this reaction they obtained 3-bromo-7-methoxy-4-methylcoumarin. Since methyl crotonate has been found to give an 86% yield of the γ-bromo derivative[13] one would expect to find that 4-methylcoumarin would act in the same manner.

Hine[14] reports that since the attacking free radical is the electropositive or electron-accepting succinimido radical, it would tend to attack a point of high electron density and avoid a point of low electron density. It is possible that the electron-withdrawing properties of the lactam group in the carbostyrils and 2-pyridones are great enough to render the 4-methyl group in the carbostyrils and the 2-pyridones (both the 4- and 6-methyl groups) too highly electropositive to allow the succinimido radical to initiate the reaction. The heterolytic reaction then takes precedence, and substitution of the bromine ultimately occurs on the ring in the 3-position of the carbostyrils and the 3- and 5-positions of the 2-pyridones. The fact that aluminum chloride catalyzes this reaction is added evidence for the heterolytic attack. Apparently the methyl groups on the 3- and 5-positions of the 2-pyridones and the 3-methyl on the carbostyril are sufficiently electronegative to allow the succinimido radical to initiate the bromine substitution on the methyl group. The fact that the methyl groups on the homocyclic ring will undergo the normal allylic bromination follows the closer similarity of the ring to the toluene system. In the case of the reaction of 4,8-dimethylcarbostyril with *N*-bromosuccinimide, the fact that the direction of the reaction can be altered by the use of either benzoyl peroxide or aluminum chloride, indicates that either mechanism will occur if the appropriate conditions are employed.

EXPERIMENTAL[15]

The infrared absorption spectra were taken on a Perkin Elmer Infracord, Model 137. The methyl-substituted carbostyrils and 2-pyridones used for the bromination studies have been prepared by previously described methods.[3,4,16-19] The various substituted methyl-2-pyridones were all converted to the *N*-methyl derivatives by the same method. A description of one compound preparation will illustrate the method.

1,6-Dimethyl-2-pyridone. A mixture of 9.7 g. (0.17 mole) of potassium hydroxide and 15.9 g. (0.15 mole) of 6-methyl-2-pyridone in 200 ml. of anhydrous ethanol was brought to reflux. Over a 2-hr. period, 28.4 g. (0.20 mole) of methyl iodide was added dropwise to the refluxing solution. Stirring and refluxing were continued for an additional 2 hr. The solution was then cooled and filtered, and the filtrate evaporated to dryness on a steam bath. The residue was extracted with chloroform, filtered, and the chloroform removed by distillation. The remaining liquid was distilled at 120–122°/2 mm. and solidified in the receiver. The product weighed 10.4 g. (56%) and after recrystallization from benzene–petroleum ether (b.p. 30–60°) melted at 55–57°. The melting point has been reported as 56.5–58°.[3]

Other *N*-methyl-2-pyridones prepared by this method are listed in Table I.

The various reactions of the substituted 2-pyridones with *N*-bromosuccinimide were all carried out under the same general conditions. A description of one compound preparation will illustrate the method.

3-Bromomethyl-1-methyl-2-pyridone (I). Two and one-half grams (0.02 mole) of 1,3-dimethyl-2-pyridone was dissolved in 35 ml. of carbon tetrachloride. After adding 3.56 g. (0.02 mole) of *N*-bromosuccinimide and 0.25 g. benzoyl peroxide to this solution, it was refluxed for 30 min. The solution was filtered hot, and the solvent removed by vacuum

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(11) A. G. Perkin, *Ann.*, **157**, 115 (1871).
(12) D. Molho and C. Mentzer, *Compt. rend.*, **223**, 1141 (1946).
(13) C. Djerassi, *Chem. Revs.*, **43**, 271 (1948).
(14) J. Hine, *Physical Organic Chemistry*, McGraw-Hill Book Co., Inc., New York, 1956, p. 430.
(15) All melting points are uncorrected.
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(17) D. J. Cook and W. C. Lawall, *J. Am. Chem. Soc.*, **70**, 1918 (1948).
(18) O. Seide, *Ber.*, **57**, 791 (1924) and *Ber.*, **57**, 1802 (1924).
(19) H. L. Bradlow and C. A. Vanderwerf, *J. Org. Chem.*, **16**, 73 (1951).

TABLE I

METHYL-SUBSTITUTED *N*-METHYL-2-PYRIDONES

2-Pyridone	Observed B.P. or M.P.	Reported B.P. or M.P.
1,3-Dimethyl-	B.p. 153–156°/30 mm.	B.p. 83–84°/1.3 mm.[19]
1,4-Dimethyl-	M.p. 58–59°	M.p. 59°[3]
1,5-Dimethyl-	B.p. 185–189°/29 mm.	B.p. 109–111°/2 mm.[19]

TABLE II

N-BROMOSUCCINIMIDE BROMINATION OF SUBSTITUTED 2-PYRIDONES

Starting Material 2-Pyridone	Product 2-Pyridone	Equiv. of NBS	Catalyst	Recryst. Solvent	M.P.	Calcd., % Br	Calcd., % N	Found, % Br	Found, % N	Yield, %	Alcoholic $AgNO_3$ Test
1,3-Dimethyl-	3-Bromomethyl-1-methyl- (I)	1	Benzoyl peroxide	Petroleum ether	98–99	39.6	6.94	39.7	7.00	45–50	Positive
1,5-Dimethyl-	5-Bromomethyl-1-methyl- (II)	1	Benzoyl peroxide	Benzene–petroleum ether	119	39.6	—	39.4	—	Low	Positive
4-Methyl-	3,5-Dibromo-4-methyl- (V)	2	Benzoyl peroxide	95% Ethanol	196–197	59.9	—	59.9	—	75	Negative
1,4-Dimethyl-	3,5-Dibromo-1,4-dimethyl- (III)	2	Benzoyl peroxide	95% Ethanol	215–216	56.9	—	56.7	—	45	Negative
1,6-Dimethyl-	3,5-Dibromo-1,6-dimethyl- (IV)	2	Benzoyl peroxide	95% ethanol	153–154[a]	56.9	—	57.0	—	57	Negative
1-Methyl-	3,5-Dibromo-1-methyl- (VI)	2	Aluminum chloride	Benzene–petroleum ether	185–187[b]	—	—	—	—	79	Negative

[a] A mixed melting point with the *N*-methyl derivative of the known 3,5-dibromo-6-methyl-2-pyridone[3] gave no depression. [b] The compound has been reported as melting at 186–187°[8] and 182–183°.[19]

distillation. After recrystallization of the residue from petroleum ether, a 45–50% yield was obtained.

The results of the various brominations of 2-pyridones with *N*-bromosuccinimide are listed in Table II.

Bromination of 2-pyridones by reaction with bromine in acetic acid. 4-Methyl, 1,4-dimethyl-, 1,6-dimethyl-, and 1-methyl-2-pyridones were dissolved in the minimum amount of glacial acetic acid, and the theoretical amount of bromine dissolved in 75% acetic acid was added dropwise to the solutions. After heating on a steam bath for 25 min., the products were recovered by pouring the acetic acid solutions onto ice and filtering. After recrystallization from ethanol-water and then benzene–petroleum ether, the 3,5-dibromo-substituted products were obtained in yields of 75–90%. Each product was the same as obtained by the action of *N*-bromosuccinimide on the pyridone.

5-Bromo-3-methyl-2-pyridone. (VII). Two and two-tenths grams (0.02 mole) of 3-methyl-2-pyridone was dissolved in 10 ml. of glacial acetic acid, and 3.6 g. (0.02 mole) of bromine in 10 ml. of 75% acetic acid was added dropwise. The mixture was heated on the steam bath for 15 min. and then poured over cracked ice. After recrystallization from benzene–petroleum ether, the white needles melted at 166–167°. The compound would not react with alcoholic silver nitrate and gave no acetoxy derivative.

Anal. Calcd. for C_6H_6ONBr: Br, 42.6. Found: Br, 42.5.

The various reactions of the substituted carbostyrils with *N*-bromosuccinimide were all carried out under the same general conditions as with the 2-pyridones with one change. Due to the decreased solubility of the carbostyrils as compared to the pyridones, the reactions were carried out in 100 ml. of carbon tetrachloride. The solutions were filtered hot, cooled, and filtered to obtain the brominated carbostyrils.

The results are contained in Table III.

4-Bromomethylcarbostyril. (XI). In a manner described by Hasegawa[7] 15 g. of acetoacetanilide (0.085 mole) dissolved in 15 ml. of chloroform was treated dropwise with 13.5 g. (0.085 mole) of bromine contained in 15 ml. of chloroform and heated on a steam bath for 30 min. After removal of the chloroform, the resulting oil was poured into 50 ml. of concd. sulfuric acid and after cooling was poured over 800 ml. of ice. The product was recrystallized from ethanol and was found to decompose at 255–256°. This is the same melting point as reported by Hasegawa. Infrared in $cm.^{-1}$ (Nujol): 1675 s, 752 s, 868 m.

4-Acetoxymethylcarbostyril. Following the procedure of Hasegawa[7] the acetoxy derivative of 4-bromocarbostyril was prepared. The m.p. of 212° was the same as that previously reported.

4-Hydroxymethylcarbostyril. One gram (0.0053 mole) of 4-acetoxymethylcarbostyril dissolved in 50 ml. of 10% potassium hydroxide was heated on the steam bath for 6 hr. Upon making the solution acidic and cooling, a product was obtained which melted at 265°. Recrystallization of this compound from ethanol gave a m.p. of 271–272° and was found to be the same as that obtained for the compound prepared from the sodium borohydride reduction of 4-formylcarbostyril.[20]

Anal. Calcd. for $C_{10}H_9O_2N$: N, 8.00. Found: N, 7.92.

4-Bromomethyl-1-methylcarbostyril. (X). A sample of 4-hydroxymethyl-1-methylcarbostyril was prepared,[20] and 0.25 g. of it was placed in 10 ml. of phosphorous tribromide and heated to 110–120° for 3 hr. The hot mixture was poured into 100 ml. of ice water and stirred until the phosphorous tribromide had hydrolyzed. The suspension was heated to boiling and filtered. Upon cooling a white solid was recovered which melted at 185–190°. Recrystallization of this substance from ethanol-water gave a m.p. of 188–191°. The same compound was obtained by the method of Hasegawa[7] when *N*-methylacetoacetanilide was treated with bromine in carbon tetrachloride to give ω-bromo-*N*-methylacetoacetanilide which upon ring closure gave a compound melting at 189–192°; a mixed melting point gave no depression. Infrared in $cm.^{-1}$ (Nujol): 1651 s, 753 s, 720 m, 904 w.

Anal. Calcd. for $C_{11}H_{10}ONBr$: N, 5.56. Found: N, 5.60.

3-Bromomethyl-4-methylcarbostyril via the Hunsdiecker reaction. 3-(4-Methylcarbostyril) acetic acid was prepared by the method of Raman[21] and found to melt at 284–285°. The silver salt of this acid was prepared by the general method of Barns and Prochaska.[22] Five grams of this salt was suspended in 50 ml. of carbon tetrachloride, and a equivalent amount of bromine was added dropwise to the refluxing solution. After heating for 2 hr., the solution was evaporated to near dryness. Extraction of the residue with ethanol-water and crystallization from this solution gave a product which melted at 187–189°. A mixed melting point with the product prepared by the action of *N*-bromosuccinimide on 3,4-dimethylcarbostyril showed no depression.

4-Bromomethyl-1,3-dimethylcarbostyril. (XV). *N*-Methyl-α methylacetoacetanilide was prepared by the previously described method,[17] and 12.5 g. (0.062 mole) of this compound was dissolved in 10 ml. of chloroform. Nine and six-tenths grams (0.062 mole) of bromine dissolved in 25 ml. of chloroform was added dropwise to the solution. The mixture was stirred at room temperature for 10 min. and then at reflux for 15 min. The chloroform was removed, and the oil poured into 50 ml. of concd. sulfuric acid. The mixture was heated on the steam bath for 30 min. and then poured into ice water. After neutralization with sodium carbonate, the solid product was obtained by filtration. The solid was extracted with hot benzene, Norite added, filtered, and cooled. Ligroin was added to the benzene solution until turbid and upon cooling, tan crystals weighing 5.1 g. (23%) were obtained. A recrystallization from 1:1 benzene-ethanol solution gave a melting point of 193–194°. The compound gave an immediate reaction with alcoholic silver nitrate, and when mixed with a sample of 3-bromomethyl-1,4-dimethylcarbostyril the melting point was depressed to 156–160°.

Anal. Calcd. for $C_{12}H_{12}ONBr$: N, 5.26. Found: N, 5.41.

8-Acetoxymethyl-4-methylcarbostyril. This compound was prepared by the method described by Hasegawa.[4] It was found to melt at 192–194°.

Anal. Calcd. for $C_{13}H_{13}O_2N$: N, 6.06. Found: N, 6.32.

4-Methyl-8-hydroxymethylcarbostyril. One gram (0.0043 mole) of 8-acetoxymethyl-4-methylcarbostyril was treated with a potassium hydroxide solution as described above. The tan precipitate melted at 195–196°. The yield was 95%. Infrared in $cm.^{-1}$ (Nujol): 1665 s, 3480 m, 1016 m, 863 m, 752 m, 746 m.

Anal. Calcd. for $C_{11}H_{12}O_2N$: N, 7.38. Found: N, 7.56.

4-Bromomethyl-8-methylcarbostyril. (XVII). Twenty grams (0.108 mole) of acetoacet *o*-toluidide was dissolved in 30 ml. of chloroform and 17.1 g. (0.108 mole) of bromine dissolved in 10 ml. of chloroform was added at a rate to keep the reaction temperature under 50°. The reaction mixture was stirred for 2 hr. at room temperature, and after removal of the solvent, the oil was poured into 100 ml. of concd. sulfuric acid at a rate to maintain the reaction temperature below 50°; the mixture was then heated on a steam bath for 15 min. After cooling and dilution with 800 ml. of ice water, the solution was neutralized with potassium carbonate and allowed to stand overnight. The precipitate was collected, dried, and found to weigh 22.1 g. (80%). After recrystallization from benzene-ethanol, white crystals melting at 236–238° were obtained. A mixed melting point with 8-bromomethyl-4-methylcarbostyril was depressed to 205–215°. Infrared in $cm.^{-1}$ (Nujol): 1652 s, 753 s, 738 m, 874 w, 802 w.

Anal. Calcd. for $C_{11}H_{10}ONBr$: N, 5.56. Found: N, 5.13.

3,4-Dibromodihydro-1,4-dimethylcargostyril. (XX). Two

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TABLE III

N-BROMOSUCCINIMIDE BROMINATION OF SUBSTITUTED CARBOSTYRILS

Starting Material Carbostyril	Product Carbostyril	Equiv. of NBS	Catalyst	Recryst. Solvent	M.P.	N, % Calcd.	N, % Found	Infrared Analysis (Nujol) in Cm.$^{-1}$	Yield, %	Alcoholic $AgNO_3$ Test
4-Methyl-	3-Bromo-4-methyl- (VIII)	1	Benzoyl peroxide	Alcohol, HOAc-water	268–269[a]	5.88	5.80	–	57[b]	Negative
1,4-Dimethyl-	3-Bromo-1,4-dimethyl- (IX)	1	Benzoyl peroxide	95% Ethanol	173[c]	—	—	s 1649, 750	82[b]	Negative
1,4-Dimethyl-3-bromo-	4-Bromomethyl-3-bromo-1-methyl- (XII)	1	Benzoyl peroxide	Petroleum ether	185–186	4.24	4.13	—	54	Positive
3,4-Dimethyl-[g]	3-Bromomethyl-4-methyl- (XIII)	1	Benzoyl peroxide	95% Ethanol	189–190[d]	5.56	5.48	s 1649, 754	53	Positive
1,3,4-Trimethyl-	3-Bromomethyl-1,4-dimethyl- (XIV)	1	Benzoyl peroxide	Benzene–petroleum ether	181–182	5.26	5.42	s 1640, 752	60	Positive
4,8-Dimethyl-	8-Bromomethyl-4-methyl- (XVI)	1	Benzoyl peroxide	Ethanol benzene	237–238[e]	5.56	5.60	s 1650, 863 s 753, 741	50	Positive
4,8-Dimethyl-	3-Bromo-4,8-dimethyl- (XVIII)	1	Aluminum chloride	95% Ethanol	239–242 dec.	5.56	5.68	s 1651 m 763, 746	79[f]	Negative
1,4,7-Trimethyl-[h]	7-Bromomethyl-1,4-dimethyl- (XIX)	1	Benzoyl peroxide	Benzene–petroleum ether	174–175	5.26	5.40	s 1650 m 873, 822	61	Positive

[a] This compound has been reported as melting at 273–275°.[5] [b] The yield was increased and reaction time decreased when aluminum chloride was used as the catalyst. [c] This compound has been reported as melting at 173°.[5] [d] A mixed melting point with the same compound prepared *via* the Hunsdiecker reaction gave no depression. [e] A mixed melting point with compound XVII melted at 205–215°. [f] Only 30% with no catalyst. [g] A. L. Searles and H. G. Lindwall, *J. Am. Chem. Soc.*, **68**, 988 (1945). [h] D. J. Cook, R. S. Yunghans, R. T. Moore, and B. E. Hoogenboom, *J. Org. Chem.*, **22**, 211 (1957).

and one-half grams (0.015 mole) of 1,4-dimethylcarbostyril was dissolved in chloroform and heated on a steam bath with 2.7 g. (0.015 mole) of bromine. After removing the excess chloroform and recrystalling from carbon tetrachloride, 4.0 g. (80%) of orange needles melting at 165–170° dec. were obtained. Warming the compound with 50 ml. of water and recrystalling from alcohol gave the known 3-bromo-1,4-dimethylcarbostyril which melted at 174–176°.

Anal. Calcd. for $C_{11}H_{11}ONBr_2$: Br, 48.0. Found: Br, 48.3.

3,4-Dibromodihydro-1-methylcarbostyril. (XXI). In a similar manner as described for the above compound, 4.0 g. (0.025 mole) of 1-methylcarbostyril was dissolved in carbon tetrachloride and heated on the steam bath with 4.5 g. of bromine for 15 min. A yellow compound melting at 142–147° was obtained. When a sample of this compound was heated with pyridine for 15 min., diluted with water, and the excess pyridine removed under vacuum, an oil was obtained. Crystallization of this oil from petroleum ether gave the known 3-bromo-1-methylcarbostyril which melted at 147–149°. Decker reported a m.p. of 149°.[23]

Anal. Calcd. for $C_{10}H_9ONBr_2$: Br, 50.2. Found: Br, 50.0.

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GREENCASTLE, IND.

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Pyrrolidines. V. 3-Pyrrolidinylmethylamines and Quinoline Derivatives[1]

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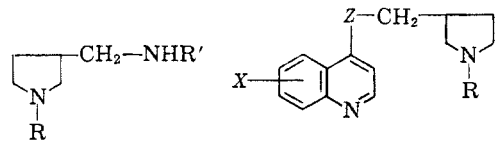
Treatment of methyl 1-substituted 5-oxo-3-pyrrolidinecarboxylates with ammonia or methylamine furnished 1-substituted 5-oxo-3-pyrrolidinecarboxamides which were reduced with lithium aluminum hydride to 1-substituted 3-pyrrolidinylmethylamines. The latter were incorporated into 4-(1-substituted 3-pyrrolidinylmethylamino)quinolines. 4-(1-Substituted 3-pyrrolidinylmethoxy)quinolines were also prepared. The reaction of itaconate esters with methanolic ammonia to furnish 5-oxo-3-pyrrolidinecarboxamide is discussed in the light of earlier literature reports.

1 - Substituted 3 - pyrrolidinylmethylamines (I) were considered key intermediates for the synthesis of potential pharmacodynamic and chemotherapeutic agents. In the present work we wish to report the synthesis of these amines and their incorporation into 4-(1-substituted 3-pyrrolidinylmethylamino)quinolines (IIa). The isosteric 4-(1-substituted 3-pyrrolidinylmethoxy)quinolines (IIb) were also prepared.

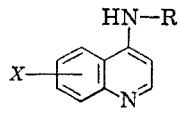


I II

IIa. Z = NH or CH_3N; IIb. Z = O; X = 6-CH_3O or 7-Cl

R = alkyl or arylalkyl

R′ = H or CH_3



IIIa. R = $CH_2CH_2N(CH_3)_2$; X = 6-CH_3O·Theophylline

IIIb. R = $CH(CH_3)(CH_2)_3N(C_2H_5)$; X = 7-Cl.

Quinolines substituted in the 4-position with a dibasic function have found divergent utilities as medicinal agents. Phthalamaquin (III-a) has found application as a bronchodilator,[2] while Chloroquin (III-b) is used as an antimalarial and anti-inflammatory agent.[3] In the present work, the terminal nitrogen of the 4-diamino function has been incorporated into a 3-pyrrolidinylmethyl ring system.[4]

Dimethyl itaconate proved to be a versatile intermediate for the synthesis of I. It has previously been shown that the reaction of dimethyl itaconate with primary amines yields methyl 1-substituted 5-oxo-3-pyrrolidinecarboxylates (IV).[5] In the present work, the latter were treated, without isolation, with ammonia or with methylamine to form 1-substituted 5-oxo-3-pyrrolidinecarboxamides (V) in good yields (Table I). Lithium aluminum hydride reduction in tetrahydrofuran then furnished the desired 1-substituted 3-pyrrolidinylmethylamines (I) (Table II).

(1) Paper IV, Y. H. Wu, J. R. Corrigan, and R. F. Feldkamp, *J. Org. Chem.*, 26, 1531 (1961).

(2) (a) C. F. Geschickter, *Southern Med. J.*, 48, 497 (1955). (b) C. F. Geschickter and L. M. Rice, Brit. Patent 773,753.

(3) J. P. Young, *Ann. Int. Med.*, 51, 1159 (1959).

(4) (a) Fr. 1,001,411 (Rhone-Poulenc) describes 4-(1-substituted 3-piperidylmethylamino)quinolines. (b) T. R. Norton *et al.*, *J. Am. Chem. Soc.*, 68, 1330 (1946), report 4-(2-piperidylmethylamino)-7-chloroquinoline by reaction of 4,7-dichloroquinoline with 2-piperidinylmethylamine.

(5) Y. H. Wu and R. F. Feldkamp, *J. Org. Chem.*, 26, 1519 (1961).