4-Methylfluorenol, VIII.—A mixture of 0.445 g. of VII, 2 g. of zinc dust, 20 cc. of ethanol and 3 cc. of 28% ammonium hydroxide was refluxed for two and a half hours. The hot mixture was filtered and the filtrate poured onto ice. The precipitate, which contained some unchanged ketone, was dried and recrystallized from benzene–petroleum ether. The first crop gave 0.210 g. (47%) of colorless very fine needles, m. p. 160–162.5°, which when recrystallized from benzene had a melting point of 164.0–164.6°. *Anal.* Calcd. for $C_{14}H_{12}O$: C, 85.67; H, 6.16. Found: C, 84.78; H, 6.18. The mother liquor was chromatographed on a 1:1 mixture of alumina and Super-Cel. The yellow band on elution gave 0.085 g. of unchanged ketone, m.p. 90.5–91.5°. Longer refluxing with intermittent addition of ammonium hydroxide did not increase the yield.

4-Methylfluorene, III.—Reduction of 0.120 g. of VIII with red phosphorus and iodine[15] gave, after recrystallization from methanol–water, 0.055 g. (50%) of III, m. p. 71.5–72.5°

Summary

When 2,2′-dimethylbiphenyl is repeatedly passed over a palladium–charcoal catalyst at 450° it is converted to 4-methylfluorene.

The synthesis of 4-methylfluorenone and its reduction to 4-methylfluorene are described.

(16) Miller and Bachman, THIS JOURNAL, **57**, 2448 (1935).

PITTSBURGH, PA. RECEIVED OCTOBER 6, 1944

[CONTRIBUTION FROM THE AVERY LABORATORY OF CHEMISTRY OF THE UNIVERSITY OF NEBRASKA]

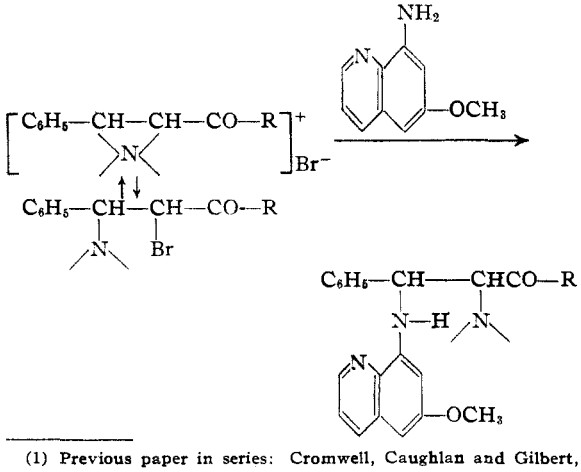
α,β-Diamino Ketones. III.[1] Reaction of 8-Amino-6-methoxyquinoline with α-Bromo-β-aminoketones

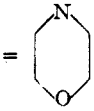
BY NORMAN H. CROMWELL AND HERMAN HOEKSEMA[2]

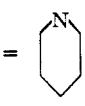
α-Bromo-β-aminoketones have been found to react readily with various heterocyclic secondary amines but less readily with open chain secondary amines[1] to give mixed diamino ketones. It was also shown that a primary amine might be used in these reactions.[3]

Since certain of the diamino ketones which have resulted from these investigations have shown mild activity as avian antimalarials it seemed important to attempt to introduce the plasmoquin base group into these molecules by treating various α-bromo-β-aminoketones with 8-amino-6-methoxyquinoline,[4] with the hope that such antimalarial activity might be enhanced.

8-Amino-6-methoxyquinoline, which is a relatively weak base, reacted quite readily with a series of α-bromo-β-aminoketones to give good yields of the desired mixed diamino ketones.



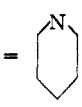
I, N =  R = C_6H_5

II, N =  R = C_6H_5

III, N = C_6H_5——CH_2, R = C_6H_5

CH_3—N

IV, N =  R = CH_3

V, N =  R = CH_3

Although the entering amino group has always been shown to take the β-position in these molecules, it seemed necessary to prove by hydrolysis that one of these, namely (I), actually had the structure assigned. On acid hydrolysis (I) gave only the expected products, benzaldehyde, 8-amino-6-methoxyquinoline and ω-morpholino-acetophenone, isolated as the oxime.

Plasmoquin base was not strong enough to react with α,β-dibromobenzylacetone or with α-bromobenzalacetone under the usual conditions. In an attempt to convert the keto to a hydroxy group in (V), only non-resolvable oils resulted from catalytic hydrogenation using palladium on charcoal or platinum oxide in glacial acetic acid solutions. These diamino ketones seem quite resistent to reduction by any of the usual methods. Moreover, it was impossible to add the methyl Grignard reagent to (IV) to form the diamino tertiary carbinol, although such additions have been accomplished with certain of the diamino ketones mentioned in previous papers.[5] The carbonyl group seems to be quite hindered in many of these diamino ketones.

Unsuccessful attempts were made to introduce

(1) Previous paper in series: Cromwell, Caughlan and Gilbert, THIS JOURNAL, **66**, 401 (1944).

(2) Parke, Davis and Co. Research Fellow, 1943–1944.

(3) Cromwell, Harris and Cram, THIS JOURNAL, **66**, 134 (1944).

(4) A supply of this base was generously furnished for this work by the Parke, Davis and Co. Research Laboratories, Detroit, Michigan.

(5) (a) Cromwell, THIS JOURNAL, **62**, 3470 (1940). (b) Unpublished work from this Laboratory.

TABLE I

PHYSICAL AND ANALYTICAL DATA

Mixed diamino ketones	No.	M. p., °C., dec.	Yield, %	Formula	Percentage composition Calcd. C	Calcd. H	Found C	Found H
β-(N-8-amino-6-methoxyquinoline)-benzylacetophenones								
α-Morpholino-[a]	(I)	194	77	$C_{29}H_{29}N_3O_3$	74.49	6.25	74.04	6.27
α-Piperidino-	(II)	183	87	$C_{30}H_{31}N_3O_2$	77.40	6.71	77.24	6.78
α-N-Methylbenzylamino-[b]	(III)	192	44	$C_{33}H_{31}N_3O_2$	79.01	6.23	78.89	6.32
β-(N-8-amino-6-methoxyquinoline)-benzylacetones								
α-Morpholino-	(IV)	159	51	$C_{24}H_{27}N_3O_3$	70.91	6.94	70.90	6.62
α-Piperidino-[c]	(V)	160	66	$C_{25}H_{29}N_3O_2$	74.43	7.24	74.47	7.29

[a] Calcd.: N, 8.98. Found: N, 9.07. [b] Calcd.: N, 8.37. Found: N, 8.19. [c] Calcd.: N, 10.42. Found: N, 10.50.

two other pharmacologically important amino groups into such molecules by treating α-bromo-β-morpholinobenzylacetone with 2-aminopyridine and with 2-aminopyrimidine, respectively. In both cases abnormal reactions[6] took place involving decomposition of the bromo amino ketone. From the former reaction mixture was isolated only α,β-dimorpholinobenzylacetone,[5] from the latter reaction mixture only the starting materials could be recovered. These experiments serve as examples of further limitations in the application of these reactions.

The diamino ketones reported here have been studied in a preliminary way as avian antimalarials and the results will be published elsewhere. Preliminary pharmacological "screening" tests,[7] (*i. e.*, pressor, analgesic, anticonvulsant, etc.) have shown no outstanding effects.

Experimental[8]

α-Morpholino-β-(N-8-amino-6-methoxyquinoline)-benzylacetophenone. (I).—α-Bromo-β-morpholinobenzylacetophenone[9] (9.0 g., one equiv.) was suspended in 35 ml. of absolute alcohol. At room temperature 8.35 g. (two equiv.) of 8-amino-6-methoxyquinoline was added to this suspension. After ten minutes of boiling the solid material in the suspension dissolved and a new precipitate formed immediately. After standing for ten hours at room temperature and for two days in the ice chest the mixture was filtered and the precipitate washed with cool absolute alcohol. The precipitate was removed from the filter and boiled with water to dissolve away the orange colored 8-amino-6-methoxyquinoline hydrobromide and the insoluble pale yellow product filtered off. This product was recrystallized, first from a chloroform–alcohol mixture and then from a benzene–petroleum ether mixture to give 9.0 g. of pale-yellow, fine needles. After drying under vacuum at 130° for three hours, the product melted at 193–194°.

By essentially this same procedure, (II) was prepared from α-bromo-β-piperidinobenzylacetophenone[10] and (III) from α-bromo-β-N-methylbenzylaminobenzylacetophenone.[11]

Hydrolysis of (I).—The diamino ketone (I) (3.0 g.) was heated on the steam-bath for two hours with 20 ml. of 15% sulfuric acid. The mixture was cooled and extracted with ether to remove the benzaldehyde and the acidic layer made basic with dilute sodium hydroxide to precipitate an oil. The oil was removed and dissolved in a small amount (5 ml.) of methyl alcohol. This solution was then added to a solution of 100 ml. of methyl alcohol, 10 g. of potassium hydroxide and 3 g. of hydroxylamine hydrochloride. After standing for five days at room temperature the methyl alcohol was removed by evaporation *in vacuo* and 25 ml. of water added to the residue. The resulting solution was extracted with ether and the water layer neutralized with dilute hydrochloric acid to form a white precipitate. After recrystallization from methyl alcohol and water, 0.10 g. of white crystals was obtained, m. p. 147–149°. A mixture of this product with an authentic sample of ω-morpholinoacetophenone oxime[12] gave no melting point depression.

α-Morpholino-β-(N-8-amino-6-methoxyquinoline)-benzylacetone (IV).—Fifteen grams (one equiv.) of α-bromo-β-morpholinobenzylacetone[5a] was suspended in 50 ml. of absolute alcohol and 16.3 g. (two equiv.) of 8-amino-6-methoxyquinoline added with slight cooling. After the suspended solid dissolved, a new precipitate appeared. The reaction mixture was allowed to stand thirty minutes at room temperature and two days in the ice chest. The product was isolated as before and recrystallized, first from a chloroform–petroleum ether mixture and then from boiling absolute alcohol to give 10 g. of white, fluffy crystals, m. p. 158–159°.

Following this same procedure (V) was prepared from α-bromo-β-piperidinobenzylacetone.[11]

Summary

1. Five new mixed diamino ketones containing the 8-amino-6-methoxyquinoline group have been prepared for antimalarial testing.

2. The carbonyl group in such mixed diamino ketones has been shown to resist some of the usual carbonyl reactions.

3. Certain limitations in the reactivity of α-bromo-β-aminoketones have been indicated.

LINCOLN, NEBRASKA RECEIVED OCTOBER 6, 1944

(6) Cromwell and Cram, THIS JOURNAL, **65**, 301 (1943).

(7) The pharmacology of these compounds is being investigated by L. W. Rowe and E. R. Loew of the Parke, Davis and Company Research Laboratories.

(8) All m. p.'s were obtained by placing the sample in the bath about 10° below the m. p. and heating at the rate of 3° per minute. Micro-Dumas analyses for nitrogen and semimicro carbon–hydrogen analyses are by the Analytical Laboratory, Department of Chemistry, University of Nebraska, under the supervision of H. Armin Pagel.

(9) Cromwell, THIS JOURNAL, **62**, 2897 (1940).

(10) Dufraisse and Moureu, *Bull. soc. chim.*, [IV] **41**, 466 (1927).

(11) Cromwell and Witt, THIS JOURNAL, **65**, 308 (1943).

(12) Cromwell and Hoeksema, *ibid.*, **66**, 870 (1944).