[CONTRIBUTION FROM STERLING-WINTHROP RESEARCH INSTITUTE AND RENSSELAER POLYTECHNIC INSTITUTE]

The Preparation and Reactions of Some α-(4-Quinolyl)-phenylacetonitriles[1]

BY ROYAL A. CUTLER, ALEXANDER R. SURREY AND JOHN B. CLOKE

The object of the present investigation was the preparation of a variety of α-(4-quinolyl)-phenylacetonitriles and products derived therefrom to make them available for pharmacological testing.

The nitriles described in this paper were prepared by the condensation of phenylacetonitrile and α-substituted phenylacetonitriles with 4-chloro, 4,5-dichloro[2] and 4,7-dichloroquinolines.[2] Inasmuch as most of the preliminary experimental work was carried out with compounds derived from 4,7-dichloroquinoline, the following discussion will be confined mainly to this series.

The condensation of 4,7-dichloroquinoline (I) with phenylacetonitrile (II) to give α-(7-chloro-4-quinolyl)-phenylacetonitrile (III) was tried under a variety of conditions in order to obtain optimum yields. When the condensation of I and II with sodamide was carried out according to the procedure of Hancock and Cope[3] for the preparation of cyclohexylphenylacetonitrile, excessive decomposition occurred at the high temperatures employed; at temperatures below 35° no decomposition was apparent. However, only a 50% yield of the nitrile (III) was obtained and half of the 4,7-dichloroquinoline was recovered. It was observed that during the reaction a red precipitate formed which appeared to be the sodio derivative of III. The formation of such a derivative at the expense of the sodio salt of the less acidic phenylacetonitrile would explain the recovery of half of the dichloro compound. The explanation is apparently correct for, when I was allowed to react with two moles each of sodamide and phenylacetonitrile, practically quantitative yields of III resulted. This procedure was equally effective with other 4-chloroquinolines.

On standing in concentrated sulfuric acid at room temperature for fifteen hours, the nitrile (III) was converted quantitatively to α-(7-chloro-4-quinolyl)-phenylacetamide (IV). An attempted preparation of α-(7-chloro-4-quinolyl)-phenylacetic acid by hydrolysis of the nitrile (III) in refluxing aqueous potassium hydroxide yielded only amide[4] (IV). Complete hydrolysis of the nitrile (III) or the amide (IV) by refluxing for one hour with 60% sulfuric acid[5] resulted in the formation of 4-benzyl-7-chloroquinoline (V). The synthesis of 4-benzylquinoline by this method is simpler and gives superior yields to those described in the literature for its preparation.[6] The methiodides of the 4-benzylquinolines (VI) were prepared by the general method described by Alekseeva.[7] It is interesting to note that, whereas no difficulty was encountered in the preparation of the unsubstituted and 7-chloro-4-benzylquinoline methiodides, attempts to dry the 5-chloro compound overnight in a vacuum desiccator resulted in its decomposition. The presence of a strong odor of benzaldehyde indicated that oxidation had occurred at the methylene group.

The preparation of esters of α-(7-chloro-4-quinolyl)-phenylacetic acid by alcoholysis of the corresponding nitrile was unsuccessful when attempted by customary procedures. Thus, on refluxing the nitrile (III) with concentrated sulfuric acid and absolute ethanol for three hours, about 90% of the starting material was recovered unchanged. Extension of the refluxing time to twenty-two hours resulted in a practically quantitative yield of 7-chloro-4-benzylquinoline (V). Similarly, when dry hydrogen chloride was passed into a refluxing solution of the nitrile in absolute alcohol for four hours, a mixture consisting of some unchanged nitrile (III), amide (IV) and 4-benzyl-7-chloroquinoline (V) was obtained. After a period of eight hours, only the benzylquinoline (V) was recovered.

The passage of dry hydrogen chloride for six hours into a solution of the nitrile (III) in absolute methanol, initially at room temperature and without external cooling, gave a quantitative yield of the amide (IV). However, when the nitrile was added to a previously saturated solution of methanolic hydrogen chloride cooled to room temperature and the passage of hydrogen chloride continued for six hours, a 12% yield of the desired methyl ester (VII) was obtained, the remainder of the product consisting of amide (IV). By allowing the reaction mixture to stand for six days at room temperature, 23% of the theoretical amount of ester resulted.

It is well known that the hydrochloride of imido esters (see Chart II, C), intermediates in the alcoholysis of nitriles in the presence of hydrogen

(1) This paper is an abstract of a thesis submitted by Royal A. Cutler to the Faculty of Rensselaer Polytechnic Institute in partial fulfillment of the requirements for the degree, Doctor of Philosophy, June, 1947. The experimental work was carried out in the laboratories of Sterling-Winthrop Research Institute. The paper was presented before the Organic Division at the Washington, D. C., meeting of the American Chemical Society on August 30, 1948.

(2) Surrey and Hammer, THIS JOURNAL, **68**, 113 (1946).

(3) Hancock and Cope, *Org. Syntheses*, **25**, 25 (1945).

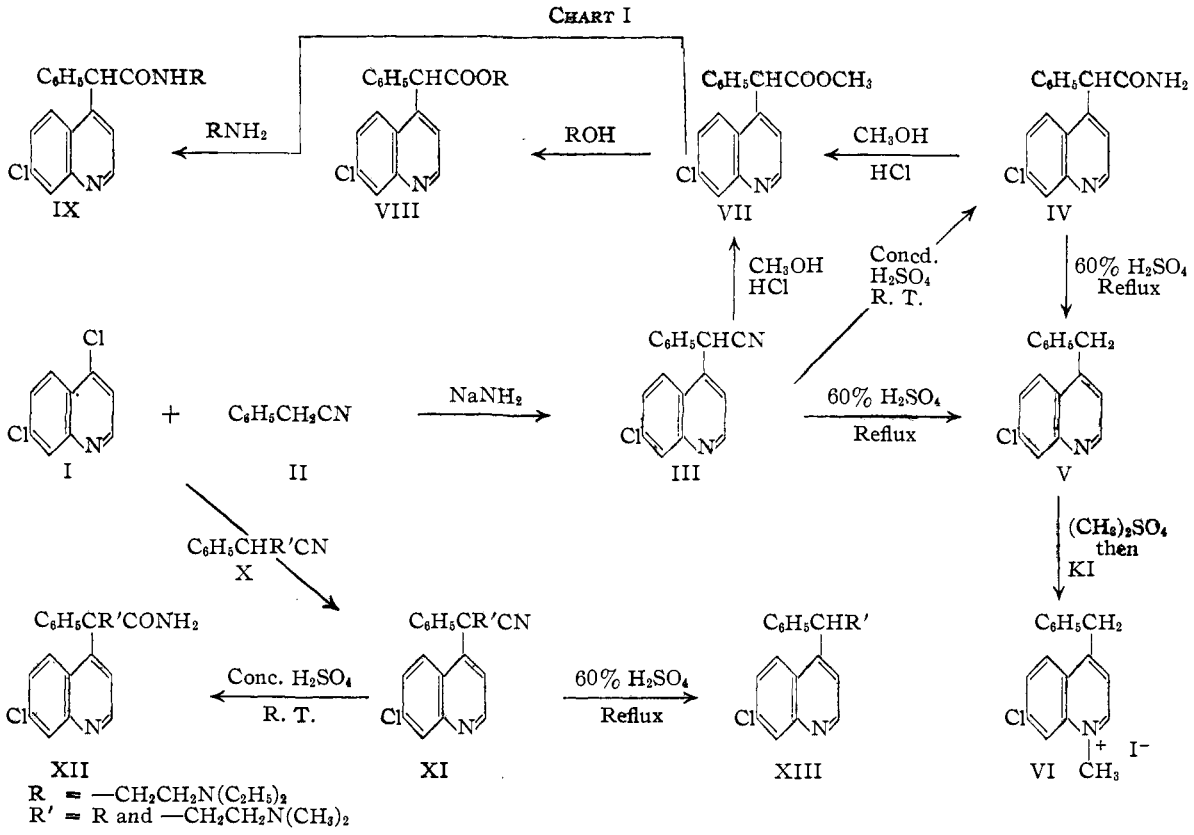
(4) It is interesting to note that when the nitrile (III) was hydrolyzed by means of sodium hydroxide and 75% ethanol, the sodium salt of IV separated from the reaction mixture in the form of pale pink needles. Treatment of this product with dilute hydrochloric acid gave the free amide (IV).

(5) When 80% sulfuric acid was used, a 40% yield of a monosulfonated 4-benzyl-7-chloroquinoline was obtained in addition to the expected product. The position of the sulfonic acid group was not determined.

(6) (a) Rabe and Pasternack, *Ber.*, **46**, 1026 (1913); (b) Bergmann and Rosenthal, *J. prakt. Chem.*, **135**, 267 (1932); (c) Dirstine and Bergstrom, *J. Org. Chem.*, **11**, 55 (1946).

(7) Alekseeva, *J. Gen. Chem.* (*U. S. S. R.*), **10**, 263 (1940); *C. A.*, **34**, 7291[5] (1940).

CHART I

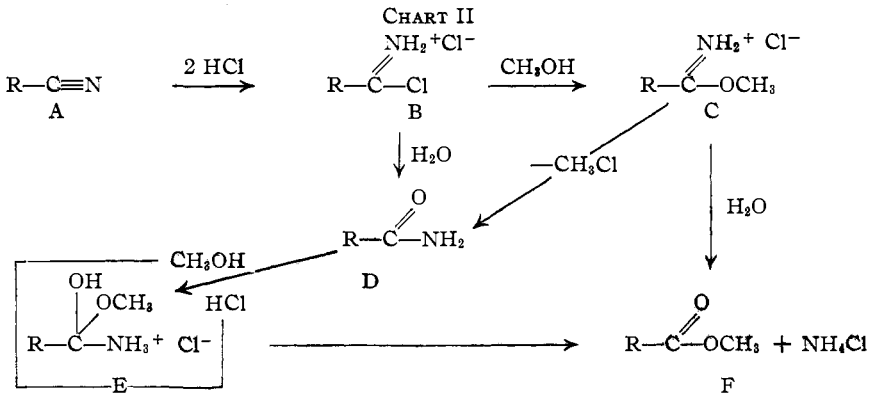


R = $-CH_2CH_2N(C_2H_5)_2$
R′ = R and $-CH_2CH_2N(CH_3)_2$

chloride, lose the elements of alkyl halide upon heating to give amides (D).[8] The kinetics of this reaction for a number of imido ester hydrochlorides have been studied.[9] Furthermore, it has been demonstrated that the presence of highly negative groups in the position alpha to the nitrile group increases greatly the ease with which this type of reaction occurs. Thus trichloroacetonitrile,[10a] dichloroacetonitrile[10b] and nitroacetonitrile[10c] when treated with hydrogen chloride in methanol split out methyl chloride from the intermediate imido ester hydrochlorides, even at temperatures below 0°, to form the corresponding amides.

It was apparent, therefore, that in the alcoholysis of the nitrile (III) the negativity of the 4-quinolyl group combined with that of the phenyl group was sufficiently great to facilitate the split of methyl or ethyl chloride even at room temperature.[11] This accounts satisfactorily for the formation of large amounts of amide (IV) in the above-described experiments.

CHART II



Consideration of the mechanism for the formation of esters (F) from the intermediate imido ester hydrochloride (C) indicates that a molecule of water is necessary for the removal of the imido group by hydrolysis. In the usual alcoholysis of nitriles, this water is provided by pouring the

(8) (a) Pinner, *Ber.*, **16**, 352 (1883); (b) Pinner, "Die Imidoäther und ihre Derivate," R. Oppenheim, Berlin, 1892.

(9) Hartigan and Cloke, THIS JOURNAL, **67**, 709 (1945).

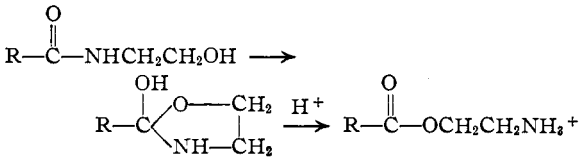
(10) (a) Steinkopf, *Ber.*, **40**, 1643 (1907); (b) Steinkopf and Malinowski, *ibid.*, **44**, 2898 (1911); (c) Steinkopf, *ibid.*, **42**, 617 (1909).

(11) The ease of formation of amide under non-hydrolytic conditions is shown by treating an ice-cooled solution of nitrile (III) in dry chloroform containing two equivalents of absolute ethanol with dry hydrogen chloride and allowing the solution to stand for three days at room temperature. The hydrochloride of the amide separated in quantitative yield.

reaction mixture into water after the imido ester hydrochloride has been formed. In the present series of nitriles (III), the intermediate imido methyl ester hydrochloride is too unstable to permit this type of treatment.[12] However, it was found that when water was incorporated into the reaction mixture, the rate of ester formation was materially increased. For example, when the nitrile (III) was added at room temperature to a solution of one part water and three parts of methanol, previously saturated with hydrogen chloride, and the passage of hydrogen chloride continued for six hours, a 32% yield of ester (VII) was obtained. On standing at room temperature for three days the yield was increased to 40% and after a period of three weeks to 70%.[13]

These results appear to indicate, according to the scheme outlined in Chart II, that the initial ester (F) formation results primarily from the hydrolysis of the imido ester hydrochloride (C). A considerable amount of amide (D) is formed concurrently due to the competing reactions; namely, the loss of methyl chloride from the imido ester hydrochloride (C) and probably also from the hydrolysis of some of the intermediate imido chloride hydrochloride (B). After the initial reaction, alcoholysis of the amide (D), to yield additional ester, proceeds at a slower rate. In order to test the latter hypothesis, the amide (IV) was subjected to the same conditions as described for the nitrile (III) to give an 18% yield of ester after six days and a 56% yield after three weeks. On employing anhydrous alcohols as the solvent a 7% yield of ester resulted from the amide after standing six days. The lower yield in the anhydrous media is probably due to the relative insolubility of the amide hydrochloride in this medium.

The alcoholysis of amides has been described previously. It is known that certain amides of β-aminoethanol rearrange in alcoholic solution under the influence of hydrogen chloride to give esters of β-aminoethanol. A possible mechanism for this type of reaction has been postulated by Phillips and Baltzly.[14] It was found that this reaction occurred rapidly even at room temperature. In one instance they reported an interconversion between the amide and ethanol, an example which still more closely resembles the present case. The authors found that, when the ethanolamide of phenylacetic acid was warmed with ethanolic hydrogen chloride, ethyl phenylacetate was obtained as one of the products.



Similar reasoning applied to the present problem would postulate that addition of methanol in the presence of excess hydrogen chloride would give the unstable addition compound, E (chart II). Loss of an ammonium ion would give the ester (F).

As an alternate method for the synthesis of ethyl α-(7-chloro-4-quinolyl)-phenylacetate, the condensation of ethyl phenylacetate with 4,7-dichloroquinoline was considered. The carbethoxylation of ethyl phenylacetate in 64% yield with ethyl carbonate or in 30% yield with ethyl chloroformate by means of sodamide in liquid ammonia has been reported.[15]

In the present work, 4,7-dichloroquinoline, ethyl phenylacetate and sodamide were stirred together at room temperature in dry benzene. After the temperature of the reaction mixture had risen to 50°, cooling was applied and the stirring continued overnight. From the reaction were isolated 20% of α-(7-chloro-4-quinolyl)-phenylacetamide (IV), about 1% of the desired ester (VII), a small amount of phenylacetamide and a 50% yield of ethyl α,γ-diphenylacetoacetate.[16] Apparently the ester is quite readily converted to the amide (IV) in the presence of sodamide. In order to avoid this latter action, sodium hydride was tried as the condensing agent. A mixture of sodium hydride, ethyl phenylacetate and 4,7-dichloroquinoline was refluxed for three hours in benzene to give a 75% yield of ethyl α,γ-diphenylacetoacetate and unchanged 4,7-dichloroquinoline. However, when a dilute benzene solution of ethyl phenylacetate was dropped very slowly into refluxing benzene containing 4,7-dichloroquinoline and an excess of sodium hydride, a 10% yield of ethyl α-(7-chloro-4-quinolyl)-phenylacetate was obtained. Inasmuch as suitable reaction conditions for the preparation of VII as well as for the corresponding ethyl ester by the alcoholysis of the nitrile (III) were finally worked out, as previously described, work on the above reaction was not pursued further.

Diethylaminoethyl α-(7-chloro-4-quinolyl)-phenylacetate (VIII) was prepared by the reaction of the corresponding methyl ester with diethylaminoethanol in refluxing Skellysolve E according to the procedure described by Surrey[17] for the *trans*-esterification of some methyl 4-quinolylmercaptoacetates. The presence of a trace of sodium decreased materially the reaction

(12) The imido ethyl ester hydrochloride is more stable. By passing hydrogen chloride into an absolute ethanol solution of the nitrile for six hours at 25° or into an aqueous-alcoholic solution cooled in an ice–salt-bath, the imido ester was obtained in good yield.

(13) The rate of alcoholysis of the nitriles in the three series studied showed a considerable variation. The rates in the order of decreasing velocity are as follows: unsubstituted > 7-chloro > 5-chloro. In the latter series only 56% of the ester was formed after five weeks whereas in the unsubstituted series a 90% yield of the ester was obtained after seventeen days.

(14) Phillips and Baltzly, THIS JOURNAL, **69**, 200 (1947).

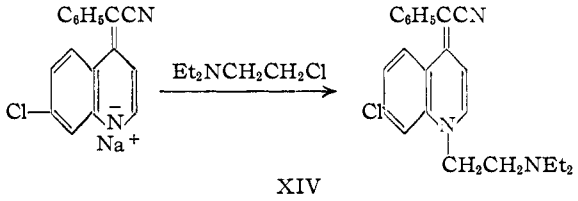
(15) Walker, Levine, Kibler and Hauser, *ibid.*, **68**, 672 (1946).

(16) A number of condensing agents have been used to prepare this compound. Its preparation in 82% yield by means of sodamide has recently been reported by Shivers, Dillon and Hauser, *ibid.*, **69**, 119 (1947).

(17) Surrey, *ibid.*, **70**, 2190 (1948).

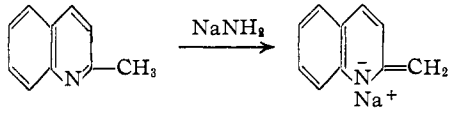
time and increased the yields. N-Diethylaminoethyl α-(7-chloro-4-quinolyl)-phenylacetamide (IX) was prepared similarly from the ester (VII) and N,N-diethylethylenediamine. The reaction was much slower than for the basic ester and was still slower in the presence of a trace of sodium. On the other hand, the presence of a little acid effectively catalyzed this reaction.

Attempts to prepare γ-diethylamino-α-(7-chloro-4-quinolyl)-phenylbutyronitrile (XI) by the condensation of the nitrile (III) with diethylaminoethyl chloride were unsuccessful. Instead, an isomeric compound was isolated in poor yield as its red-orange hydrochloride. The free base crystallized from Skellysolve B in two forms: namely, ruby-colored rectangular plates and long orange rods melting at 102–103° and 84–85°, respectively. These could be separated by mechanical means but on recrystallization either of the two forms again gave a mixture of the two crystalline modifications. The structure of the base is probably that of the N-alkylated compound (XIV) derived from the sodium salt whose structure is very likely that shown below.



XIV

Bergstrom[18] reported a similar type of salt formation in the case of 2-alkylquinolines. Treatment of the latter with alkali amides in liquid ammonia resulted only in salt formation with the enamic modification.



The preparation of γ-diethylamino-α-(7-chloro-4-quinolyl)-α-phenylbutyronitrile (XI) was accomplished in excellent yields by the condensation of 4,7-dichloroquinoline with γ-diethylamino-α-phenylbutyronitrile (X)[19] in the presence of sodamide. In addition it was found that phenyllithium in ether or sodium hydride in refluxing benzene also brought about the condensation.

Treatment of the nitrile (XI) with concentrated sulfuric acid at room temperature for four to five weeks gave a 90% yield of the amide (XII). After standing for three days only a 15% yield of XII was obtained. XII also resulted in 15% yield from refluxing the nitrile (XI) with sodium hydroxide in 70% ethanol for twelve hours. When the nitrile (XI) was refluxed with 60% sulfuric acid for one hour a 15% yield of the amide (XII) was isolated; after refluxing for twelve hours, a practically quantitative yield of 7-chloro-4-(3-diethylamino-1-phenylpropyl)-quinoline (XIII) was obtained. As would be expected, the rates of hydrolysis of the nitrile (XI) were much slower than for III. In the preparation of 5-chloro-4-(3-diethylamino-1-phenylpropyl)-quinoline, some of the intermediate amide was still present after refluxing for forty-eight hours.

(18) Bergstrom, *ibid.*, **53**, 3027 (1931).

(19) Eisleb, *Ber.*, **74**, 1433 (1941).

Experimental[20]

α-(7-Chloro-4-quinolyl)-phenylacetonitrile (III).[21]—One hundred and ten grams (2.6 moles) of sodium amide[22] was added to a well-stirred, ice-cooled solution of 260 g. (2.2 moles) of phenylacetonitrile in one liter of dry benzene contained in a flask fitted with a soda-lime tube. The temperature rose gradually to 35° and the color of the solution changed from a pale yellow to a deep reddish black. After stirring for an hour, one mole (198 g.) of 4,7-dichloroquinoline was added portion-wise at a rate sufficient to maintain the temperature at 25–30° with strong external cooling. After the addition was complete, the ice-bath was removed and the reaction mixture stirred at room temperature for two hours. The bright red sodium salt of the product and excess sodium amide were decomposed by the cautious addition of water by means of a dropping funnel. The light reddish-orange benzene layer was washed once with water, followed by extraction with three 500-cc. portions of 9 *N* hydrochloric acid.[23] Ice was added to the acid extracts and the free base liberated by the addition of concentrated ammonium hydroxide. The red oil which formed was taken up in chloroform and dried over Drierite. Removal of the solvent gave a viscous oil which on treatment with ether and scratching yielded a pale yellow solid. In the case of IIIa[24] the oil was distilled at 0.1 micron, b. p. 140°, and the bright red distillate crystallized from a mixture of Skellysolve A and ether. Subsequent runs required no distillation.

The crude solids were obtained in practically quantitative yields and were used in subsequent reactions without further purification. Analytical samples were obtained by recrystallization from Skellysolve B or C.

α-(7-Chloro-4-quinolyl)-phenylacetamide (IV).—One part by weight of α-(7-chloro-4-quinolyl)-phenylacetonitrile was dissolved in four volumes of concentrated sulfuric acid and, after standing overnight at room temperature, the solution was poured into ice containing an excess of ammonium hydroxide. The solid amide was obtained in quantitative yield. Recrystallization from butanol gave a white crystalline solid. In the case of IVb,[24] ethanol was used as the recrystallization solvent.

7-Chloro-4-benzylquinoline (V).—Five parts by weight of the nitrile (III) and eight parts by volume each of concentrated sulfuric acid and water were refluxed vigorously for one hour. During the initial part of the reaction, carbon dioxide was evolved in copious amounts. At the end of the reaction, the yellow solution was poured onto ice

(20) All melting points are uncorrected. All analyses were performed by Mr. Auerbach and staff of these laboratories. Nitrogen, unless otherwise specified, was determined by means of a modified Kjeldahl procedure. Chlorine analyses, exceptions noted, were performed by means of the Parr-bomb method.

(21) The experimental procedures listed represent those for the compounds derived from 4,7-dichloroquinoline. The compounds in the unsubstituted and 5-chloro series were also prepared according to these methods with but few modifications which are noted.

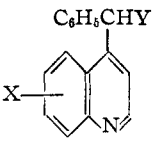
(22) The sodamide used was prepared in the factory of Winthrop-Stearns, Inc. The granular material was stored under toluene and ground under benzene or toluene before use. The resulting finely divided material was pressed out between filter papers and quickly weighed, an excess being used in each case to make allowance for any solvent present.

(23) 6 *N* Hydrochloric acid was used for IIIa (see Table I). In the case of IIIb the solid hydrochloride tends to form during the extraction and may cause difficulty during separation.

(24) See Table I.

TABLE I

α-(4-QUINOLYL)-PHENYLACETONITRILES AND RELATED COMPOUNDS



No.	X	Y	Yield,[a] %	M. p., °C.	Empirical formula	Analyses, % Chlorine Calcd.	Chlorine Found	Nitrogen Calcd.	Nitrogen Found
IIIa	H	-CN	76[b]	86-86.5	$C_{17}H_{12}N_2$	...	...	11.47	11.38
IIIb	5-Cl	-CN	100	149.5-150.5	$C_{17}H_{11}ClN_2$	12.72	12.52	10.05	10.00
III	7-Cl	-CN	90[b]	117.5-118.5	$C_{17}H_{11}ClN_2$	12.72	12.46	10.05	9.97
IVa	H	$-CONH_2$	100	267-268	$C_{17}H_{14}N_2O$	...	...	10.68	10.49
IVb	5-Cl	$-CONH_2$	96	212-213	$C_{17}H_{13}ClN_2O$	11.95	12.09	9.44	9.42[c]
IV	7-Cl[d]	$-CONH_2$	100	283-284	$C_{17}H_{13}ClN_2O$	...	...	9.44	9.49
Va	H[e]	-H	95	52-52.5	$C_{16}H_{13}N$	[f]	...	6.39	6.23
Vb	5-Cl	-H	98	51-51.5	$C_{16}H_{12}ClN$	13.97	13.74	5.52	5.63
V	7-Cl	-H	98	93.5-94	$C_{16}H_{12}ClN$	13.97	13.91	5.52	5.31
VIIa	H	$-COOCH_3$	90	60.5-61.5	$C_{18}H_{15}NO_2$	[g]	...	5.05	5.04[h]
VIIb	5-Cl	$-COOCH_3$	56	114-114.5	$C_{18}H_{14}ClNO_2$	...	...	4.49	4.48[h]
VII	7-Cl	$-COOCH_3$	70	127-127.5	$C_{18}H_{14}ClNO_2$	11.37	11.49	4.49	4.49[h]
VIIIa	H	-COOR[i]	75	136-137[j]	$C_{23}H_{26}N_2O_2 \cdot HCl$	8.89	8.89[k]	[l]	
VIIIb	5-Cl	-COOR[i]	72	174-175[j]	$C_{23}H_{25}ClN_2O_2 \cdot HCl$	16.36	16.20	6.47	6.25
VIII	7-Cl	-COOR[i]	86	155.5-156.5[j]	$C_{23}H_{25}ClN_2O_2 \cdot HCl$	16.36	16.38	6.47	6.25
IXa	H[m]	-CONHR[i]	6[n]	117.5-118	$C_{23}H_{27}N_3O$	...	...	11.63	11.50[c]
IX[b]	5-Cl[o]	-CONHR[i]	22[p]	92-93	$C_{23}H_{26}ClN_3O$	...	...	7.08	7.03[h]
IX	7-Cl[q]	-CONHR[i]	65[r]	132.5-133	$C_{23}H_{26}ClN_3O$	8.96	8.95	10.62	10.41

[a] Yields based on amount of crude product. Losses from purification amounted to from 5–15% in most instances. [b] Yield after crystallization of crude oil from ether. [c] Dumas nitrogen. [d] Hydrochloride, m. p. 267–268° dec.; *Anal.* Calcd. for $C_{17}H_{13}ClN_2O \cdot HCl$: Cl^-, 10.66; N, 8.40. Found: Cl^-, 10.92; N, 8.54. [e] Sulfate salt, m. p. 195–196°. *Anal.* Calcd. for $C_{16}H_{13}N \cdot H_2SO_4$: $SO_4^=$, 30.24. Found: $SO_4^=$, 30.67. [f] Calcd.: C, 87.64; H, 5.98. Found: C, 87.56; H, 5.71. [g] Calcd.: C, 77.96; H, 5.45. Found: C, 78.15; H, 5.72. [h] Titration of basic nitrogen by the method of Toennies and Callan, *J. Biol. Chem.*, **125**, 259 (1938). [i] R = $-CH_2CH_2N(C_2H_5)_2$. [j] Obtained as non-distillable oils. The melting points and analyses are those of the monohydrochlorides. [k] Ionic chlorine. [l] Calcd.: C, 69.25; H, 6.82. Found: C, 69.24; H, 6.86. [m] Monohydrochloride, m. p. 110–112°. *Anal.* Calcd. for $C_{23}H_{27}N_3O \cdot HCl$: Cl, 8.91. Found: Cl^-, 8.84. [n] Refluxed sixteen hours. Low yield due to addition of trace of sodium which inhibits this reaction. [o] Monohydrochloride, m. p. 99.5–101°. *Anal.* Calcd. for $C_{23}H_{26}ClN_3O \cdot HCl$: Cl, 16.40. Found: Cl, 16.15. [p] Refluxed twenty-six hours without catalyst. [q] Monohydrochloride, m. p. 156–157°. *Anal.* Calcd. for $C_{23}H_{26}ClN_3O \cdot HCl$: Cl, 16.40; N, 9.72. Found: Cl, 16.12; N, 9.55. [r] A trace of concentrated hydrochloric acid used as catalyst. Without catalyst the yield was 25%.

containing an excess of ammonium hydroxide. The product which separated was taken up in ether, dried over Drierite and the solvent evaporated to give a quantitative yield of a pale yellow oil which solidified on standing. Recrystallization from Skellysolve B gave long silky white needles.

In an initial experiment, 5 g. of the nitrile (III) was treated in a similar fashion using 12 cc. of concentrated sulfuric acid and 5 cc. of water. After extraction of the desired product (1.6 g.) with ether, acidification of the alkaline solution yielded 1.8 g. of a white solid which was purified by reprecipitation with acid from its sodium bicarbonate solution. Analysis indicated that it was a monosulfonated derivative of 7-chloro-4-benzylquinoline. The position of the sulfonic acid group was not determined.

Anal. Calcd. for $C_{16}H_{12}ClNO_3S$: Cl, 10.62; S, 9.60. Found: Cl, 10.51; S, 9.53.

7-Chloro-4-benzylquinoline Methiodide (VI).—The procedure was similar to the general method described by Alekseeva.[6] The product, obtained in quantitative yield, was recrystallized by stirring in 35 volumes of hot absolute alcohol followed by ice cooling, to give golden leaflets, m. p. 223–225° dec. Prolonged contact with hot alcohol results in considerable decomposition.

Anal. Calcd. for $C_{17}H_{15}ClIN$: I, 32.08; N, 3.54. Found: I, 31.60; N, 3.73.

4-Benzylquinoline methiodide obtained by the above procedure melted at 224–226° dec. (Rabe and Pasternack[6a] reported 226° dec.).

5-Chloro-4-benzylquinoline methiodide decomposed on drying in a vacuum desiccator overnight to give a dark brownish-red solid with a strong odor of benzaldehyde.

Methyl α-(7-Chloro-4-quinolyl)-phenylacetate (VII).—The following procedure gave the best yields of any method tried.

A solution of one part by volume of water in 3 parts by volume of methanol was saturated with gaseous hydrogen chloride with strong external cooling. The ice-bath was removed and one part by weight of the nitrile (III) added at 10–15°. The addition of hydrogen chloride was continued, the temperature rose to 35° and the solid soon dissolved completely to form a clear yellow solution. The white hydrochloride of the nitrile (III) soon separated and gradually redissolved over a period of two hours. (In the case of VIIa and VIIb[24] the hydrochloride of the corresponding nitrile did not separate.) The hydrogen chloride was bubbled slowly through the solution for a total of five or six hours. The resulting solution was stoppered and allowed to stand at room temperature for varying amounts of time. As ester formation occurred, ammonium chloride separated, the time required for the first appearance of this salt serving as a rough guide as to the rate of esterification. (The times required for the appearance of ammonium chloride for each of the compounds prepared were as follows: VIIa two to three hours; VII, ten to twelve hours; VIIb, about one week.) The reaction mixture was worked up by pouring into ice water and liberating the ester with aqueous sodium hydroxide in the presence of chloroform, care being taken to keep the solution cold by the addition of ice. Filtration at this point removed most of the amide present. The chloroform

layer upon separation, drying with Drierite, followed by evaporation, yielded the ester. The crude product was freed from small amounts of amide present[25] by dissolving in hot Skellysolve C (VIIb and VII) or a large volume of Skellysolve B (VIIa), filtering with charcoal, seeding and allowing to cool. The esters were recrystallized from the Skellysolves or methanol (VIIb) to give white crystalline solids. The crude yields of the three compounds prepared by this procedure are as follows: VIIa, 90% after standing seventeen days; VIIb, 56% after five weeks (yield after recrystallization from Skellysolve C); VII, 32% after six hours, 40% in three days, 70% after two weeks.

The methyl ester (VII) was also prepared from the amide (IV) by the same procedure. The yield of crude ester, after standing for six days, was 18% and 56% after three weeks.

Ethyl α-(7-Chloro-4-quinolyl)-phenylacetate.—This ester was prepared from the nitrile (III) according to the procedure outlined for the methyl ester. The yield after three days of standing was 54%, m. p., 125.5–126°, white thick needles.

Anal. Calcd. for $C_{19}H_{16}ClNO_2$: Cl, 10.88; N, 4.30. Found: Cl, 10.72; N, 4.24.

Ethyl α-(7-Chloro-4-quinolyl)-imidoacetate.—Twenty-eight grams (0.1 mole) of α-(7-chloro-4-quinolyl)-phenylacetonitrile (III) was added to 200 cc. of 95% ethanol, previously saturated with hydrogen chloride and thoroughly cooled in an ice-salt-bath. The passage of hydrogen chloride was continued with occasional shaking until solution was effected. After standing for three days in the ice-chest, the reaction mixture was diluted with two liters of ether, the resulting white crystalline precipitate collected on a filter and treated with dilute sodium bicarbonate solution. The mixture was shaken with chloroform and the insoluble amide (IV) collected on filter; yield, 5.5 g. The chloroform layer was separated from the filtrate, dried over anhydrous sodium sulfate, filtered with charcoal and the solvent removed by distillation to give 19.5 g. (0.06 mole) of almost white solid, m. p. 149–151°. Recrystallization from Skellysolve C, including treatment with charcoal, gave large white crystals, m. p. 155–157° (cor.).

Anal. Calcd. for $C_{19}H_{17}ClN_2O$: C, 70.25; H, 5.28; Cl, 10.92; N, 8.63. Found: C, 70.62; H, 5.13; Cl, 10.68; N (Dumas), 8.49.

The imido ester was also formed in good yield by adding the nitrile (III) to a saturated hydrogen chloride solution of absolute ethanol and passing in hydrogen chloride for six hours.

Diethylaminoethyl α-(7-Chloro-4-quinolyl)-phenylacetate (VIII).—A mixture of 15 g. (0.048 mole) of methyl α-(7-chloro-4-quinolyl)-phenylacetate (VII), 30 cc. of diethylaminoethanol, 110 cc. of Skellysolve E and a small piece of freshly cut sodium[26] about the size of a grain of wheat was placed in a 500-cc. round-bottomed flask fitted with a water separator, reflux condenser, and a drying tube. The mixture was refluxed (sixteen to twenty-four hours) at a rate just sufficient to allow the methanol formed in the reaction to distil over into the water separator. The cooled reaction mixture was diluted with an equal volume of ether and extracted with 0.5 *N* hydrochloric acid. The combined extracts were made just alkaline to litmus with 10% sodium hydroxide and extracted with ether to remove any unchanged ester together with small amounts of the 7-chloro-4-benzylquinoline formed due to the action of the sodium alkoxide present. The aqueous layer was then made alkaline to phenolphthalein with caustic, extracted with ether, the ether extracts dried with Drierite, and the solvent removed by distillation; yield, 16.35 g. (86%). In the case of VIIIa[24] and VIIIb the yields were 75 and 72%, respectively.

(25) In the preparation of VIIb, about one-quarter of the product at this point was amide because of the greater solubility of this compound in chloroform.

(26) A run made under similar conditions, but without sodium, gave only a 39% yield.

The free basic esters (VIIIa, VIIIb, and VIII) were all light orange-yellow oils. An attempted distillation of VIIIa was interrupted because of excessive decomposition. The mono-hydrochlorides of these compounds were readily obtained by dissolving the base in three volumes of acetone or isopropyl alcohol, adding slightly less than the calculated amount of alcoholic hydrogen chloride, diluting with ether just to turbidity and scratching or seeding to start crystal formation. Where necessary, the hydrochlorides were recrystallized from isopropyl alcohol or acetone. The hydrochlorides are stable, white crystalline substances easily soluble in water.

N-Diethylaminoethyl α-(7-Chloro-4-quinolyl)-phenylacetamide (IX).—The basic amide was prepared by the same procedure described above for the basic ester using N,N-diethylethylenediamine. In the presence of a trace of sodium the yield was 6%. Without the catalyst, the yields ranged from 20–25% and were increased to 65% when an acid catalyst (a trace of concentrated hydrochloric acid) was used. The product was recrystallized from Skellysolve B or C to give a white crystalline solid.

The monohydrochlorides of the bases (IXa,[24] IXb and IX) were prepared by the addition of slightly less than the equivalent amount of alcoholic hydrogen chloride to an isopropanol or acetone solution of the base.

Alkylation of α-(7-Chloro-4-quinolyl)-phenylacetonitrile. Preparation of XIV.—Sodamide (7 g.) was added to a stirred mixture of 40 g. of the nitrile (III) and 43 g. of diethylaminoethyl chloride in dry benzene at room temperature. The solution turned a ruby-red color as the red sodium salt of III separated. After stirring for thirty hours, the mixture was still a bright red; but, on standing for sixty hours more, it became black. After the cautious addition of water, the benzene layer was extracted with 1 *N* hydrochloric acid until the washings were but slightly colored. Evaporation of the benzene solution gave 17 g. of the starting material (III). The acid extracts were made just alkaline to congo red with sodium hydroxide, the black gum which separated was discarded and the solution filtered with charcoal to give a deep ruby-red filtrate. The latter was made alkaline to phenolphthalein, extracted with chloroform, the chloroform extracts dried over Drierite, filtered with charcoal and evaporated to give 30 g. of a black oil. This was taken up in ether, filtered from the solid which separated, and evaporated to give 20 g. of black oil which was in turn taken up in 60 cc. of isopropyl alcohol and 20 cc. of 3.6 *N* alcoholic hydrogen chloride added. On standing in the ice-chest, 2.6 g. of red needles separated. These were recrystallized from 200 cc. of isopropyl alcohol to yield 1.8 g. of fine red-orange needles, m. p. 215–216° dec. A mixed melting point with an authentic sample of γ-diethylamino-α-(7-chloro-4-quinolyl)-α-phenylbutyronitrile hydrochloride (m. p. 211–212°) melted at 175–190°. The analysis, however, indicated an isomeric compound.

Anal. Calcd. for $C_{23}H_{24}ClN_3 \cdot HCl$: Cl, 66.50; H, 6.07; Cl, 17.11. Found: C, 66.41; H, 5.97; Cl, 16.98.

Conversion of a sample of the above hydrochloride to the free base yielded a dark ruby viscous oil which was crystallized from Skellysolve B to give a mixture of dark ruby-red rectangular plates and orange rods. The two were separated by hand picking, the former melting at 102–103° and the latter at 84–85°. A mixed melting point appeared slightly moist at 82° but melted at 84–87°. Recrystallization of either solid from Skellysolve B resulted in the formation of a mixture of the two modifications. The ruby-red plates analyzed as follows:

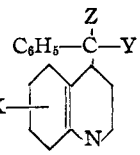
Anal. Calcd. for $C_{23}H_{24}ClN_3$: C, 73.10; H, 6.40; N, 11.12. Found: C, 73.31; H, 6.18; N, 11.11.

γ-Dialkylamino-α-(7-chloro-4-quinolyl)-α-phenylbutyronitrile (XI).[27]—To a dry benzene solution (750 cc.)

(27) The γ-diethylamino and γ-dimethylamino compounds in this series (see Table II) were prepared in the same fashion and so will be treated under the general heading, γ-dialkylamino, exceptions being noted. The general procedure used in the preparation of these nitriles is similar to that described by Cloke, *et al.*, THIS JOURNAL, **53**, 2791 (1931), and Ziegler and Ohlinger, *Ann.*, **495**, 84 (1932).

TABLE II

γ-DIALKYLAMINO-α-PHENYL-α-(4-QUINOLYL)-BUTYRONITRILES AND RELATED COMPOUNDS



							Bases					Monohydrochlorides				
							Analyses, %						Analyses, %			
				Yield,[a]		Empirical	Chlorine		Nitrogen				Chlorine		Nitrogen	
No.	X	Y	Z	%	M. p., °C.	formula	Calcd.	Found	Calcd.	Found	M. p., °C.		Calcd.	Found	Calcd.	Found
XIa	H	-CN	[b]	88	69.5–70.5	$C_{21}H_{21}N_3$	...	...	8.88	8.84[c]	224–226		[d]	...	11.94	11.69
XIb	5-Cl	-CN	[b]	86	115.5–116	$C_{21}H_{20}ClN_3$	10.13	10.12	12.01	11.87[e]	274–275		18.36	18.08	10.88	10.60
XI	7-Cl	-CN	[b]	95	104.5–105.5	$C_{21}H_{20}ClN_3$	10.13	10.12	12.01	11.82[e]	260–262		18.36	18.08	10.88	10.65
XIIa	H	$-CONH_2$	[b]	64[f]	170.5–171.5	$C_{21}H_{23}N_3O$	...	...	8.41	8.34[c]	254–255		9.59	9.48[g]	11.36	11.59[e]
XIIb	5-Cl	$-CONH_2$	[b]	91	203–204 d.	$C_{21}H_{22}ClN_3O$	9.64	9.36	11.43	11.19	221–222		8.71	8.71[g]	10.40	10.22
XII	7-Cl	$-CONH_2$	[b]	97	187–188	$C_{21}H_{22}ClN_3O$	...	...	7.61	7.58[c]	248–249		17.54	17.00	10.40	10.22
XIIIa	H	-H	[b]	97	89–89.5	$C_{20}H_{22}N_2$	...	...	9.65	9.65[c]	155.5–156.5		10.85	10.96[g]	8.57	8.25
XIIIb	5-Cl	-H	[b]	76	[h]	$C_{20}H_{21}ClN_2$	...	...	8.63	8.50[c]	195–196		9.81	9.92[g]	7.74	7.44
XIII	7-Cl	-H	[b]	97	77–78[i]	$C_{20}H_{21}ClN_2$	10.92	10.97	8.63	8.61	[j]		...	...	...	...
XIa	H	-CN	[k]	97	72.5–73[l]	$C_{23}H_{25}N_3$	...	...	12.24	12.08	211.5–212.5		9.33	9.20[g]	[m]	...
XIb	5-Cl	-CN	[k]	98	120.5–121	$C_{23}H_{24}ClN_3$	9.38	9.50	11.12	10.80	237–239		8.55	8.40[g]	10.14	9.92
XI	7-Cl	-CN	[k]	91	91–92	$C_{23}H_{24}ClN_3$	9.38	9.31	11.12	10.92	211–212		17.11	17.10	10.14	9.97
XIIa	H	$-CONH_2$	[k]	85	135–136[n]	$C_{23}H_{27}N_3O$	...	...	7.75	7.74[c]	247–248		8.91	8.70[c]	[o]	...
XIIb	5-Cl	$-CONH_2$	[k]	81	174–175	$C_{23}H_{26}ClN_3O$	8.96	9.01	10.62	10.89[e]	225–226		8.20	8.29[g]	[p]	...
XII	7-Cl	$-CONH_2$	[k]	76[f]	147.5–148.5	$C_{23}H_{26}ClN_3O$	8.96	9.03	10.62	10.48	236 d.		8.20	8.10[g]	9.72	9.57
XIIIa	H	-H	[k]	88	[q]	$C_{22}H_{26}N_2$	...	...	8.80	8.66[c]	173–174 d.		9.99	10.00[g]	7.90	7.61
XIIIb	5-Cl	-H	[k]	80	[r]	$C_{22}H_{25}ClN_2$	...	...	7.94	7.88[c]	178.5–179.5		9.11	9.12[g]	7.20	7.11
XIII	7-Cl	-H	[k]	94	[s]	$C_{22}H_{25}ClN_2$	10.05	10.00	7.94	7.70	196.6–197.5[t]		18.21	18.06	7.20	7.06

[a] Yields represent the crude products. Losses from purification amounted to from 5–15% in most cases. [b] Z = $-CH_2CH_2N(CH_3)_2$. [c] Titration of basic nitrogen. [d] Calcd.: C, 71.68; H, 6.30. Found: C, 71.66; H, 6.04. [e] Dumas nitrogen. [f] Lower yield due to accidental loss of product. [g] Ionic chlorine. [h] Yellow oil distilled at 150° at 0.1 micron; $n^{25}D$ 1.6200. [i] First obtained as a pale yellow tinted oil by distillation at 154° at 0.1 micron; $n^{25}D$ 1.6124. [j] No solid hydrochloride was obtained. [k] Z = $-CH_2CH_2N(C_2H_5)_2$. [l] Appears to exist in two crystalline modifications. When first isolated it melted at 96–104°. [m] Calcd.: C, 72.71; H, 6.90. Found: C, 72.58; H, 7.01. [n] Exists in a lower melting solvated form, m. p. 90–92°, when recrystallized from benzene. Analytical sample dried *in vacuo* for one hour at 100°. [o] Calcd.: C, 69.42; H, 7.49. Found: C, 69.47; H, 6.97. [p] Calcd.: C, 63.89; H, 6.29. Found: C, 64.39; H, 6.36. [q] Pale yellow oil; b. p. 190° at 0.5 mm.; $n^{25}D$ 1.5942. [r] Yellow oil; b. p. 209° at 0.8 mm.; $n^{25}D$ 1.6052. [s] Pale yellow oil distilled at 155–156° at 0.1 micron; $n^{25}D$ 1.5986. [t] Corrected melting point; sample immersed at 140° and bath raised 3° per minute. When the melting point is taken rapidly it melts at 158–160° (uncor.).

of the 4,7-dichloroquinoline (0.5 mole) and one-half mole of γ-dialkylamino-α-phenylbutyronitrile[28] in a two-liter, three-necked flask fitted with a stirrer, thermometer, and drying tube was added 28 g. of fresh,[29] powdered sodamide. External cooling was applied when necessary to keep the temperature of the reaction mixture below 45°. At the end of two to three hours, the temperature had dropped to room temperature and stirring was continued for an additional four to five hours. Water was added cautiously and the dark colored solution changed to a light orange color. The benzene layer was washed twice with water and dried over Drierite. It was filtered with charcoal and evaporated to give a practically quantitative yield of the base. When the base was obtained as a viscous oil, it was stirred with a little ether to induce crystallization. Recrystallization from Skellysolve B or C yielded a pure sample of white crystalline solid.

The monohydrochlorides of the basic nitriles (see Table II) were prepared by dissolving the base in three to four volumes of warm isopropyl alcohol and adding slightly less than the calculated amount of alcoholic hydrogen chloride. In some instances ether was added to turbidity and the solution scratched to induce crystallization. The hydrochlorides were dried at 120° *in vacuo*.

γ-Dialkylamino-α-(7-chloro-4-quinolyl)-α-phenylbutyramide (XII).—A solution of one part by weight of the nitrile (XI) in four volumes of concentrated sulfuric acid was allowed to stand at room temperature for four to five weeks. The yellow solution was poured onto ice, treated with an excess of sodium hydroxide solution and extracted with chloroform. The combined extracts were dried over Drierite, filtered with charcoal and the chloroform distilled to give 80% yields or better of the amides. The crude products were crystallized from benzene or toluene to give white crystalline solids.

When the nitrile (III) was allowed to stand for three days in concentrated sulfuric acid, only a 15% yield of the amide was obtained. Refluxing the nitrile with an equal weight of sodium hydroxide in eight volumes of 70% ethanol for twelve hours or by heating 5 g. of the nitrile, 8 cc. of water and 8 cc. of concentrated sulfuric acid at reflux for one hour gave approximately 15% yields of the amide.

The monohydrochlorides were prepared by a procedure similar to that used in the preparation of the corresponding salts of the basic nitriles (XI). Larger volumes (5–20) of isopropyl alcohol were required to dissolve the amides. The salts were recrystallized from ethanol and dried *in vacuo* at 140°.

7-Chloro-4-(3-dialkylamino-1-phenylpropyl)-quinoline (XIII).—A solution of 30 g. of γ-dialkylamino-α-(7-chloro-4-quinolyl)-α-phenylbutyronitrile (XI) in 50 cc. of water and 50 cc. of concentrated sulfuric acid was refluxed for twelve to forty-eight hours. In some cases, the completeness of the reaction was determined by passing nitrogen over the surface of the reaction mixture and bubbling the escaping gases through barium hydroxide solution. When no cloudiness resulted after a minute or so, the reaction was regarded as complete. The reaction mixture was poured into ice containing an excess of sodium hydroxide solution, extracted with ether, the ether dried, filtered with charcoal and evaporated to give a pale yellow oil. In the case of XIIIb, some intermediate amide was isolated even after refluxing for forty-eight hours. This

(28) γ-Diethylamino-α-phenylbutyronitrile[19] and γ-dimethylamino-α-phenylbutyronitrile (Kwartler and Lucas, THIS JOURNAL, **68**, 2395 (1946)) were prepared in about 80–90% yields by the condensation of phenylacetonitrile with diethylaminoethyl chloride and dimethylaminoethyl chloride, respectively, under conditions similar to those described for the preparation of III.

(29) The use of sodamide which had been stored under toluene for long periods of time (four to six months) gave yields as low as 20%.

was removed by dissolving the oil in Skellysolve B, seeding with amide and allowing to stand twenty-four hours. Evaporation of the filtered solution gave the desired base. These bases could be converted to the monohydrochlorides without further purification or distilled under vacuum to give pale yellow tinted oils. The latter are all quite stable to heat but on standing for several days at room temperature, where dialkyl is diethyl, the bases develop a beautiful lavender or purple color. In two instances (see Table II) the bases solidified and were recrystallized from Skellysolve B.

The monohydrochlorides were prepared by dissolving the free base in three volumes of isopropyl alcohol and adding slightly less than the equivalent amount of alcoholic hydrogen chloride. In order to induce crystallization, ether was added to turbidity, the inside of the flask scratched and the solution allowed to stand. The analytical samples were dried *in vacuo* at about 120°.

The monohydrochloride of 7-chloro-4-(3-dimethylamino-1-phenylpropyl)-quinoline could not be induced to crystallize. A dihydrochloride, m. p. 215–217°, was prepared but gave an unsatisfactory analysis.

Summary

The condensation of phenylacetonitrile with 4-chloro-, 4,5-dichloro- and 4,7-dichloroquinoline has been investigated under a variety of conditions. The resulting α-(4-quinolyl)-phenylacetonitriles were converted to the corresponding α-(4-quinolyl)-phenylacetamides and 4-benzylquinolines.

The preparation of the methyl α-(4-quinolyl)-phenylacetates from the corresponding nitriles and some basic esters and basic amides is reported.

The reaction of γ-dialkylamino-α-phenylbutyronitrile with 4-chloroquinolines is also described. The nitriles so formed were converted to the corresponding amides and 4-(3-dialkylamino-1-phenylpropyl)-quinolines.

RENSSELAER, NEW YORK RECEIVED APRIL 15, 1949

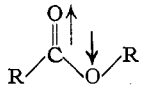
[CONTRIBUTION FROM THE COLLEGE OF PHARMACY OF THE UNIVERSITY OF CALIFORNIA AND THE RESEARCH DIVISION OF CUTTER LABORATORIES]

The Dipole Moment of Methyl Benzylpenicillinate

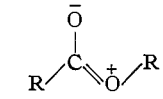
BY W. D. KUMLER, I. F. HALVERSTADT AND EDWARD L. ALPEN

Methyl benzylpenicillinate has been reported to have a dipole moment of approximately 8 from measurements in chloroform and anhydrous ethanol solutions.[1] It seems improbable that the molecule would have such a large moment if the commonly accepted structure of penicillin is correct. The large moment would mean that the individual moments were lined up in nearly the same direction, which is rather unlikely.

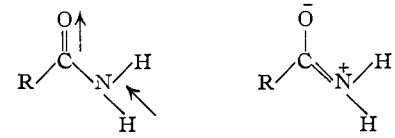
The group moments contributing to the over-all resultant moment are those of the ester (1.8), sulfide (1.6), amide (3.8)[2] and lactam (3.8 estimated). The moment of the lactam might be increased somewhat over an ordinary amide as a result of the ring formation, just as a lactone has a higher moment (4.1)[3] compared with an ester (1.8) but this increase in case of the lactam amide would be considerably less than in the case of the lactone. The ester is almost entirely in a form in which the ether dipole almost directly opposes the carbonyl dipole.



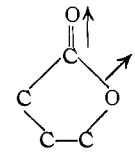
The molecule is held in this configuration by the contribution from the resonating form



which gives some double bond character to the carbonyl carbon–ether oxygen bond. The amides likewise are probably held in a similar configuration by resonance but here the moment of the amine portion (0.6–1.2) is not only smaller than that of the ether (1.3), but its resultant is not opposed to that of the carbonyl moment.



This effect is in part responsible for the dipole moment of amides being greater than that of a ketone (2.8), while that of an ester is considerably less. When an ester is bent around to form a lactone the moments are no longer directly opposed



but augment one another to some extent. However, when an amide is closed into a lactam there will not be nearly as much enhancement because there was originally not as much opposition to the

(1) O. S. R. D. Report Sh 4, 34 (1944) Shell Development Co. also the "Chemistry of Penicillin," Princeton University Press, Princeton, New Jersey, 1949, p. 407. This value was offered as an approximate value only. Although some workers interpreted this value as evidence for a zwitterion structure for penicillin, the Shell workers pointed out that although the value of 8 was intermediate between the moment of molecules without a separation of charge and the moment of zwitterion molecules, the fact that the molecule did not show a positive dielectric increment was evidence against its being a zwitterion.

(2) Kumler and Porter, THIS JOURNAL, **56**, 2549 (1934).

(3) Marsden and Sutton, *J. Chem. Soc.*, 1383 (1936).