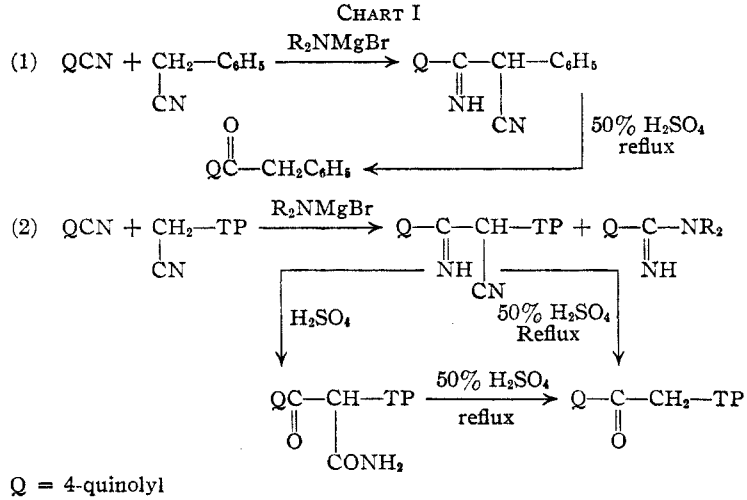
[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

The Reaction of Halogenomagnesium Dialkylamides with Nitriles. The Preparation of N,N-Disubstituted Amidines

BY EMIL LORZ AND RICHARD BALTZLY

The 4-acyl quinolines required for a variety of syntheses are usually prepared by Claisen-type condensations of ethyl cinchoninate or its derivatives with the appropriate aliphatic esters. Since cinchoninic acid is most conveniently obtained by the hydrolysis of 4-cyanoquinoline it seemed likely that a more economical synthesis would be provided by a Ziegler type condensation of 4-cyanoquinoline itself with the desired nitrile using lithium or halomagnesium dialkylamides as the condensing agents. This expectation was realized in a model experiment, phenylacetonitrile and 4-cyanoquinoline reacting in the presence of bromomagnesium dibutylamide to give in 66% yield of α-phenyl-β-(4-quinolyl)-β-imidopropionitrile from which 4-phenacetylquinoline was obtained by refluxing with sulfuric acid (50% by volume). The course of these reactions is shown by equation 1.

CHART I



Q = 4-quinolyl
TP = 4-tetrahydropyranyl

When, however, 4-tetrahydropyranacetonitrile was used in place of phenylacetonitrile the principal product obtained was a basic substance that survived refluxing with 50% sulfuric acid and which was eventually shown to be N,N-di-*n*-butylquinoline-4-carboxamidine. This substance had evidently been produced by an addition of the bromomagnesium dibutylamide to 4-cyanoquinoline, a reaction that was not anticipated since Ziegler and Ohlinger[1] reported that the metal derivatives of secondary amines did not add to nitriles. Ziegler operated exclusively with aliphatic nitriles and it would appear from examination of his procedures and comparison with our own that the addition reaction must proceed much more rapidly with aromatic nitriles than with aliphatic. Addition does take place with aliphatic nitriles, however, since in a later experiment using bromomagnesium di-*n*-amylamide, 4-cyanoquinoline and tetrahydropyranacetonitrile, a small amount of N,N-di-*n*-amyltetrahydropyran-4-acetamidine was obtained. Since the properties of this type of amidine are unfavorable for isolation it is to be presumed that homologous substances were formed in traces in other experiments also. A recent paper by Hullin, Miller and Short[2] on the synthesis of amidines by the addition of magnesium amides to nitriles lends support to this belief as these authors report the formation of N,N-diethylvaleramidine in 26% yield by the reaction of bromomagnesium diethylamide with valeronitrile.

Further investigation showed that under suitable conditions, 40–50% yields of α-tetrahydropyranyl-β-(4-quinolyl)-β-imidopropionitrile could be obtained but that 4-quinoline-N,N-dialkylcarboxamidines were also formed in comparable amounts. This finding and subsequent transformations of the imidonitrile are represented by equation 2. This picture was not significantly altered by the use of lithium dialkylamides and, after this was ascertained, the more convenient magnesium compounds were used exclusively. Since amidines were being obtained in any case, a number of preparations of the imidonitrile were made using available secondary amines in the condensation, the corresponding amidines being isolated as by-products.

The amidines XII, XIV, XVI and XVII were tested for anti-plasmodial action, of which they proved to be devoid. General pharmacological screening, however, showed the presence of local anesthetic activity. When the antimalarial program was suspended it appeared advisable to investigate the addition of halomagnesium dialkyl amides to nitriles as a preparative method and a program was initiated with the object of learning the limitations and utility of the method and also of studying the pharmacology of the amidines produced. This report is concerned primarily with the first part of the program.

During the preparation of this paper the publication of Hullin, Miller and Short[2] appeared. It

(1) Ziegler and Ohlinger, *Ann.*, **495**, 84 (1932).

(2) Hullin, Miller and Short, *J. Chem. Soc.*, 394 (1947).

deals largely with the same subject, but while our findings are in general agreement with theirs we are able to augment and extend their experiments in some respects.

Hullin, Miller and Short found this amidine preparation to be most useful when an aromatic nitrile reacted with a magnesium dialkylamide. The yield was somewhat less when the magnesium amide was derived from methylaniline and the reaction failed with bromomagnesium diphenylamide. This is in agreement with our own experiments. It would appear that the metal–nitrogen bond acquires more of a salt-like character as the acidity of the amine increases and that this sets a limit on the ability of the metal amide to behave as a nitrogen–Grignard reagent. The British authors also found the magnesium amides obtained from aniline and benzylamine to add less readily to aromatic nitriles than bromomagnesium diethylamide. This seems inconsistent with the work of Ziegler and Ohlinger in which amidine formation was prominent when bromomagnesium ethylamide reacted with dialkyl acetonitriles but was absent when bromomagnesium diethylamide was used. Each group of workers operated with nitriles of restricted variety, however, and it is probable that further investigation will resolve this inconsistency.

While we are in agreement with Hullin, Miller and Short that the addition of halomagnesium dialkylamides to aliphatic nitriles is of small preparative value, we have had somewhat more favorable experience with aromatic nitriles, the yields in such cases being generally good. In one respect this reaction is considerably superior to the classical Pinner[3] method. As might be predicted from Kadesch's[4] discussion of steric hindrance in aromatic ketones, this addition is little subject to hindrance. Whereas the Pinner method is reported to fail with *o*-tolunitrile and α-naphthonitrile[5] amidines have been prepared from both by the present procedure in satisfactory yield. Furthermore, both 2-methoxyl-1-naphthonitrile and cyanomesitylene react with bromomagnesium di-*n*-butylamide with no apparent difficulty.

If halomagnesium dialkylamides be supposed to act in essentially the same manner as a Grignard reagent, they should add to some at least of the functions characteristically vulnerable to ordinary Grignard reagents. Most of the products to be expected from such reactions, however, would be either unstable or more readily accessible by other methods. It did seem possible that the reaction $R'R^2NMgBr + RX \rightarrow RR'R^2N + MgBrX$ would be of value in the preparation of tertiary amines. This possibility was explored by refluxing *n*-butyl bromide in ethereal solution with bromomagnesium benzyl-*n*-butylamide. After three hours less than 10% of tertiary amine had been formed showing that reaction in the expected fashion was not rapid and that consequently selective alkylation was improbable.

(3) Pinner, "Die Imidoäther und ihre Derivate," Berlin, Germany, 1890.

(4) Kadesch, THIS JOURNAL, **66**, 1207 (1944).

(5) Pinner, *Ber.*, **23**, 161 (1890).

Experimental

Physical and analytical data on the amidines prepared are shown in Table I. All melting points are corrected.

General Procedure for the Addition Reactions.—To a solution of ethylmagnesium bromide containing about 50% excess Grignard reagent (on the basis of the nitrile to be used) was added gradually a slight excess of the secondary amine. Evolution of ethane generally continued for about thirty minutes.[1] The solution was then refluxed fifteen to twenty minutes further and the nitrile was added, usually in ethereal solution, but in some cases dissolved in benzene (for reasons of solubility). After the solutions had been refluxed for two to three hours or occasionally longer (as indicated in Table I), the reaction mixtures were decomposed with ice and ammonium chloride solution and worked up further according to three general procedures.

Method A.—The total material from the hydrolysis of the reaction mixture was made strongly alkaline. The amidine base and remaining secondary amine were taken into ether, dried, and separated by distillation *in vacuo*. This procedure was preferred for the more volatile amidines.

Method B.—The material from the hydrolysis of the reaction mixture was steam distilled, thereby removing unreacted nitrile and secondary amine. It was usually necessary to add some strong alkali in order to ensure volatilization of secondary amine. The residual material was then made strongly alkaline and the remaining bases were taken into ether. When quite involatile secondary amines were employed (di-octylamine) it was advantageous to extract the ethereal layer with successive inadequate amounts of dilute hydrochloric acid, a separation being thus obtained of stronger from weaker bases. The aqueous extracts were made acid to congo paper, evaporated separately *in vacuo* and the residues were crystallized from suitable solvents.

Method C.—In certain cases, the amidine base precipitated during the hydrolysis of the reaction mixture with ammonium chloride solution. The bulk of the product could thus be filtered off at this stage. It was usually necessary to partition it between dilute sodium hydroxide solution and benzene in order to free the base of small amounts of magnesium salts. The bases could then be acidified with ethanolic hydrogen chloride solution and crystallized as the hydrochlorides.

All the amidines here reported crystallized readily as the hydrochlorides though seldom in characteristic form. Most of the crystals appeared to be stubby prisms or rhombs. The acridine derivative (XI) and the dibenzylbenzamidine (XIII) were crystallized from absolute ethanol; the piperazine derivative XXIV, was crystallized from 95% ethanol. All the others were purified by crystallization from ethanol–ether mixtures.

α-Phenyl-β-(4-quinolyl)-β-imidopropionitrile.—Preliminary experiments using benzonitrile and benzyl cyanide had indicated that the best conditions for condensation were obtained when the two nitriles were added simultaneously.

To a solution of ethylmagnesium bromide prepared from 3.7 g. of magnesium and 16.5 g. (0.15 mole) of ethyl bromide in 200 cc. of ether was added 20 g. (0.155 mole) of di-*n*-butylamine. The solution was refluxed fifteen minutes after addition and a solution of 12 g. (0.1 mole) of benzyl cyanide and 15.5 g. (0.1 mole) of 4-cyanoquinoline dissolved in a mixture of benzene and anisole was added gradually. There was considerable heat of reaction and a red color appeared followed by precipitation of an orange solid. The mixture was refluxed for five hours and allowed to stand overnight. The orange precipitate was filtered off and washed with benzene. The filtrate and precipitate were hydrolyzed separately with ammonium chloride solution, the former eventually yielding 1.5 g. of the condensation product. The precipitate on hydrolysis

TABLE I

N,N-DIALKYLAMIDINE HYDROCHLORIDES, $R-\overset{NH_2\cdot Cl}{\overset{\|}{C}}-NR'_2$

No.	R	R′	Method of isolation	Yield, %	M. p., °C.	Empirical formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
I	Phenyl	*n*-Butyl	A	82[a]	174[b]	$C_{18}H_{25}ClN_2$	67.02	9.37	67.07	9.29
II	*o*-Tolyl	*n*-Butyl	A	70[a]	192[c]	$C_{16}H_{27}ClN_2$	67.94	9.62	68.19	9.80
III	*o*-Methoxyphenyl	*n*-Butyl	B	45[d,e]	161	$C_{16}H_{27}ClN_2O$	64.30	9.11	64.14	9.13
IV	*o*-Chlorophenyl	*n*-Butyl	B	83[e]	234	$C_{15}H_{24}Cl_2N_2$	59.40	7.98	59.50	8.15
V	*m*-Chlorophenyl	*n*-Butyl	B	70[e]	170	$C_{15}H_{24}Cl_2N_2$	59.40	7.98	59.40	7.90
VI	*p*-Chlorophenyl	*n*-Butyl	B	80[e]	149	$C_{15}H_{24}Cl_2N_2$	59.40	7.98	59.37	8.04
VII	*p*-Dimethylaminophenyl	*n*-Butyl	B	74[e]	197	$C_{17}H_{30}ClN_3$	65.46	9.70	65.70	9.82
VIII	Styryl	*n*-Butyl	C	55[f]	204	$C_{17}H_{27}ClN_2$	69.24	9.23	69.06	9.24
IX	1-Naphthyl	*n*-Butyl	B	72[e]	211	$C_{19}H_{27}ClN_2$	71.53	8.54	71.38	8.48
X	2-Methoxy-1-naphthyl	*n*-Butyl	C	63[d,f]	196	$C_{20}H_{29}ClN_2O$	68.84	8.38	68.83	8.45
XI	9-Acridyl	*n*-Butyl	B	69[d,e]	285 (dec.)	$C_{22}H_{28}ClN_3$	71.42	7.63	71.33	7.49
XII	4-Tetrahydropyranyl-methyl	*n*-Amyl		[g]	128	$C_{17}H_{35}ClN_2O$	64.02	11.06	63.76	11.12
XIII	Phenyl	Benzyl	C	66[f]	228	$C_{21}H_{21}ClN_2$	74.87	6.28	74.55	6.44
XIV	4-Quinolyl	Ethyl		[g]	213.5 (dec.)	$C_{14}H_{18}ClN_3$	63.75	6.88	63.92	7.00
	Base of XIV			[h]	111	$C_{14}H_{17}N_3$	73.97	7.54	74.16	7.20
XV	4-Quinolyl	*n*-Propyl	B	80[e]	266 (dec.)	$C_{16}H_{22}ClN_3$	65.85	7.60	65.87	7.58
XVI	4-Quinolyl	*n*-Butyl		[g,i]	214	$C_{18}H_{26}ClN_3$	67.57	8.20	67.66	8.47
XVII	4-Quinolyl	*n*-Amyl		[g]	151 (dec.)	$C_{20}H_{30}ClN_3$	69.11	8.72	69.00	8.80
XVIII	4-Quinolyl	*n*-Hexyl	B	69[e]	159	$C_{22}H_{34}ClN_3$	70.28	9.12	70.35	9.09
XIX	4-Quinolyl	*n*-Heptyl	B	70[e]	154–155	$C_{24}H_{38}ClN_3$	71.34	9.48	71.42	9.30
XX	4-Quinolyl	*n*-Octyl	B	60[e]	149	$C_{26}H_{42}ClN_3$	72.27	9.80	72.21	9.64
XXI	Mesityl	*n*-Butyl	B	72[e,j]	254–255	$C_{15}H_{31}ClN_2$	69.54	10.05	69.54	10.30
XXII	N-Phenyl-N-*n*-butyl benzamidine hydrochloride		A	50[a,k]	214	$C_{17}H_{21}ClN_2$	70.69	7.33	70.55	7.37
XXIII	1-Phenyl carbimido-1,2,3,4-tetrahydroquinoline hydrochloride		B	45[e]	229 (dec.)	$C_{16}H_{17}ClN_2$	70.45	6.28	70.45	6.27
XXIV	N-Benzyl-N′-phenylcarbimido piperazine dihydrochloride		C	52[f]	267 (dec.)	$C_{18}H_{23}Cl_2N_3$	61.36	6.58	61.22	6.59

[a] Yield calcd. on weight of distilled base. [b] B. p. of base, 120–121° (1 mm.). [c] B. p. of base, 140° (1 mm.). [d] The nitrile was dissolved in benzene for addition to the bromomagnesium dialkylamide. [e] Yield calcd. on weight of purified hydrochloride. [f] Yield calcd. on weight of crude base precipitated during hydrolysis of reaction mixture. [g] Obtained as byproduct in condensation. [h] Crystallized from ethyl acetate–ether mixture. [i] B. p. of base, 180–190° (1 mm.). [k] B. p. of base, 172° (1 mm.). [l] After addition of the nitrile the solution was allowed to stand for sixteen hours at room temperature and refluxed five hours longer. Allowing for recovered cyanomesitylene, the yield was 93%.

changed to a sandy solid which was washed successively with methanol and ether, wt. 16.5 g. This substance after crystallization from alcohol formed cream-colored prisms, m. p. 189–190°.

Anal. Calcd. for $C_{18}H_{13}N_3$: C, 79.67; H, 4.83, Found: C, 79.80; H, 5.15.

4-Phenacetylquinoline.—On addition of 5.5 g. of the imidonitrile to a solution of 25 cc. of concd. sulfuric acid and 25 cc. of water an orange-red solid (presumably a sulfate) precipitated. The mixture was heated cautiously at first as there was considerable frothing. The red color faded gradually being succeeded by a deep yellow. After four hours of refluxing the solution was cooled and basified with sodium carbonate. A yellow oil separated which solidified and was recrystallized first from dilute methanol, then from ether–hexane mixture. It then formed colorless rectangular plates melting at 89–89.5°.

Anal. Calcd. for $C_{17}H_{13}ON$: C, 82.53; H, 5.30. Found: C, 82.62; H, 5.50.

α-(4′-Tetrahydropyranyl)-β-(4-quinolyl)-β-imidopropionitrile.—To a solution in 200 cc. of ether of ethylmagnesium bromide prepared from 10 g. of magnesium and 43.6 g. (0.4 mole) of ethyl bromide was added 51.6 g. (0.4 mole) of di-*n*-butylamine. The solution was refluxed for one-half hour and a solution in 400 cc. of 50% anisole–benzene of 30.8 g. (0.2 mole) of 4-cyanoquinoline and 25.2 g. (0.203 mole) of tetrahydropyran-4-acetonitrile was added rapidly. The reaction mixture was refluxed one-half hour (longer reaction times affected the yield adversely) and poured into a solution of 40 g. of ammonium chloride in 200 cc. of ice water. At this stage a faint but definite odor of hydrogen cyanide could be noted. A considerable amount of solid (the imidonitrile) separated at this point and was filtered off and washed with water and ether. The combined filtrates and washings were steam-distilled and the residue was extracted with ether. A further portion of imidonitrile separated during this extraction and was added to the earlier crop. The ethereal extract was dried over potassium carbonate and yielded, on acidification with ethanolic hydrogen chloride, 20 g. of crude N,N-di-*n*-butyl cinchoninamidine hydrochloride (XVI).

The imidonitrile obtained from the hydrolysis of the reaction mixture (weight, 28.6 g.) was not free of magnesium, was very high-melting and virtually insoluble in organic solvents. When dissolved in iced 3 *N* hydrochloric acid and cautiously basified it could be obtained substantially pure.

Anal. Calcd. for $C_{17}H_{17}N_3O$: C, 73.07; H, 6.14. Found: C, 72.79; H, 6.43.

α-(4′-Tetrahydropyranyl)-β-(4-quinolyl)-β-oxopropionamide.—Five grams of the imidonitrile was allowed to stand overnight at room temperature with 8 cc. of concd. sulfuric acid and 2 cc. of water. In the morning the resultant solution was poured onto ice. A light yellow pre-

cipitate formed which was collected and crystallized from absolute ethanol, m. p. 211° (dec.).

Anal. Calcd. for $C_{17}H_{19}N_2O_2 \cdot H_2SO_4$: C, 51.36; H, 5.33; N, 7.06. Found: C, 51.30; H, 5.19; N (Dumas), 6.99.

4-Quinolyl-4'-tetrahydropyranylmethyl Ketone.—Twenty-eight grams of the crude imidonitrile was allowed to stand for two days with 100 cc. of concd. sulfuric acid. The solution was then diluted with 100 cc. of water and the whole was refluxed five hours. The mixture was cooled, diluted and basified with sodium carbonate. The precipitated oil was taken into ether, dried over potassium carbonate and acidified with 48% hydrobromic acid. The hydrobromide crystallized from absolute ethanol as yellow plates melting at 214° (dec.).

Anal. Calcd. for $C_{16}H_{18}NO_2 \cdot HBr$: C, 56.97; H, 5.68. Found: C, 56.75; H, 5.73.

In our hands the bromination of both 4-phenacetyl quinoline and the corresponding tetrahydropyranyl ketone proved quite unsatisfactory. A number of products were isolated but their identity was dubious and they proved valueless for synthetic purposes.

Acknowledgment.—The authors wish to express their gratitude to Messrs. Walter S. Ide and Samuel W. Blackman for the micro-analyses here recorded.

Summary

1. The condensations of 4-cyanoquinoline with benzyl cyanide and tetrahydropyrane-4-acetonitrile using halomagnesium dialkylamides as condensing agents have been studied. While feasible, these condensations appear inferior to the more usual ester condensations, a marked complication being amidine formation between the condensing agent and the aromatic nitrile.

2. The additions of halomagnesium dialkyl or alkyl aryl amides to aromatic nitriles proceed readily and with good yields, thus constituting a useful synthesis of N,N-disubstituted amidines. A particular advantage of the reaction is its relative independence of steric hindrance.

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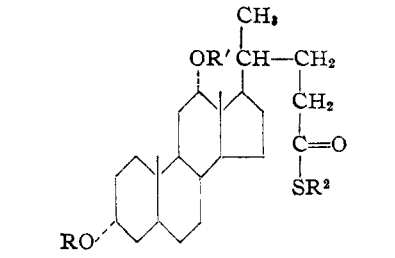
Steroid Acids and Their Transformation Products. II. Desulfurization of Thiol Esters of Desoxycholic Acid[1a]

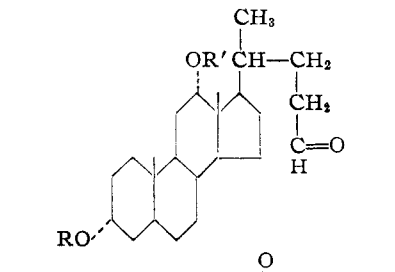
BY GEORGE B. SPERO, A. VERN MCINTOSH, JR., AND ROBERT H. LEVIN

The preparation of a number of thiol esters of steroid acids, including ethyl 3(α),12(α)-diformoxythiolcholanate (Ia),[1b] was reported recently.[2] According to the literature desulfurization of thiol esters with Raney nickel catalyst may yield alcohols[3] or aldehydes.[4] In our laboratory the course of the desulfurization of I was found to be dependent on the character of the Raney nickel catalyst. Using freshly prepared standard Raney nickel[5] the ethyl thiol ester (Ia) was converted to the cholane alcohol (III) and traces of the cholanic aldehyde (II). These results were obtained with 60 to 90% alcohol as a solvent, reflux times of one to five hours, and a ratio of 5 to 20 g. of catalyst per gram of thiol ester. When the more active W-4 Raney catalyst[6] was used, the thiol ester (Ia) was rapidly and quantitatively reduced and desulfurized to the alcohol (III). Karabinos[7] has suggested that if the reaction is interrupted immediately after the thiol ester has disappeared (as tested by odor after acidification) a good yield of



Ia, R = R' = $\overset{O}{\overset{\|}{C}}$—H; $R^2 = C_2H_5$

b, R = R' = $\overset{O}{\overset{\|}{C}}$—H; $R^2 = CH_2C_6H_5$



IIa, R = R' = $\overset{O}{\overset{\|}{C}}$H

b, R = H; R' = $\overset{O}{\overset{\|}{C}}$H

c, R = R' = H

(1a) Presented before the Division of Medicinal Chemistry at the 112th A. C. S. Meeting, New York, September, 1947.

(1b) Formulation of desoxycholic acid as 3(α),12(α) is according to the latest stereochemical evidence. For a discussion see the review article by Reichstein and Reich, *Ann. Rev. Biochem.*, **15**, 162 (1946).

(2) Levin, McIntosh, Spero, Rayman and Meinzer, THIS JOURNAL, **70**, 511 (1948).

(3) (a) Prelog, Norymberski and Jeger, *Helv. Chim. Acta*, **29**, 360 (1946); (b) Jeger, Norymberski, Szpilfogel and Prelog, *ibid.*, **29**, 684 (1946); (c) Ruzicka, Szilfogel and Jeger, *ibid.*, **29**, 1520 (1946).

(4) Wolfrom and Karabinos, THIS JOURNAL, **68**, 1455 (1946).

(5) Adkins, "Reactions of Hydrogen with Organic Compounds over Copper–Chromium Oxide and Nickel Catalysts," The University of Wisconsin Press, Madison, Wis., 1937, p. 20.

(6) Pavlic and Adkins, THIS JOURNAL, **68**, 1471 (1946).

(7) Private communication.