[Contribution from Kedzie Chemical Laboratory, Michigan State University]

A Study of the Alkylation of Hydratroponitrile with Amyl Halides[1]

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The alkylation of hydratroponitrile with various amyl halides has been investigated. Chlorides and bromides appear equally satisfactory as alkylating agents; iodides are less satisfactory. The structure of the alkyl halide affects the yield of product, the yields decreasing in the order iso ⋝ secondary > normal ≫ tertiary. *tert*-Amyl chloride dehydrohalogenates under the condition of the reaction. The difficulty of hydrolysis of the highly branched nitriles which are formed in this alkylation may be correlated in a semiquantitative manner using the *six-number* concept of Newman.

Nitriles possessing one or two α-hydrogen atoms can be mono- or di-alkylated in the presence of a base such as sodamide according to the equation

$$RCH_2CN \xrightarrow[NaNH_2]{R^1X} RR^1CHCN \xrightarrow[NaNH_2]{R^2X} RR^1R^2CCN$$

An extensive survey of the literature concerning this alkylation reaction has revealed that, although quite a number of such reactions have been recorded, most of the reports are from different laboratories and the reactions have been carried out under varying conditions. Hence it is quite difficult to compare the yields and determine their dependence on reaction conditions. Recently Hauser and Brasen[2] have published a paper concerning the relative amounts of monoalkylation and dialkylation of phenylacetonitrile with several alkyl halides.

A previous paper from this laboratory[3] has reported the results of the alkylation of hydratroponitrile (α-phenylpropionitrile) with the butyl halides. This paper presented evidence showing that the yield of alkylated hydratroponitrile was not influenced appreciably by the halogen of the alkyl halide. However, the structure of the alkyl group did affect the yields, causing them to decrease in the order iso ⋝ secondary > normal ≫ tertiary. Tilford and co-workers[4,5] have prepared a number of alkylated cyclohexylcyanides, the alkyl groups containing from four to eight carbon atoms, using sodamide in liquid ammonia. Their results indicate that their yields were affected by the alkyl halide and decreased in the order normal > iso > secondary. Since the previous study[3] was limited in scope and since the results were not in complete agreement with those of the latter workers, it appeared desirable to investigate the alkylation of hydratroponitrile further. The amyl halides were selected for this purpose.

The results of this alkylation study are shown in Table I. Since excellent results had been obtained with the butyl *chlorides* in the earlier work, the amyl chlorides were selected as the preferred alkylating agents. A few bromides and one iodide were also included for comparison. The high temperature alkylation procedure of Ziegler and Ohlinger[6] was utilized throughout and an attempt was made to duplicate the conditions and equipment used previously so that the results would be comparable. The chlorides appear to give slightly better yields than the bromides. The run with *n*-amyl iodide gave free iodine, which made purification of the final product difficult. As observed in the earlier work[3] the branched chain and secondary halides gave somewhat higher yields than did the normal amyl halide. *tert*-Amyl chloride gave only a trace of a solid alkylation product.

TABLE I

YIELDS OF ALKYLATED HYDRATROPONITRILES

Halide	Yield, %[a]	B.P. Range, °C.	mm
n-Amyl chloride	78	111–116	4
	77	122–142	4–6
n-Amyl bromide	76	128–132	6
n-Amyl iodide	60.0 (73)[b]	119–123	4
Isoamyl chloride	85	107–110	2–3
	84	110–120	2–4
1-Chloro-2-methylbutane	90[c]	97–99	*ca.* 1
	90[c]	97–99	*ca.* 1
2-Chloropentane	69 (88)[b]	106–120	2
2-Bromopentane	84	98–101	1
3-Chloropentane	88	106–116	2–1
	84	103–108	*ca.* 1
Chlorocyclopentane	90	117–120	1–2
	86	115–120	1–2
tert-Amyl chloride	Trace	118–132[d]	2
	Trace	113–148[d]	1
	Trace[e]	119–124[d]	2

[a] Based on initial weight of hydratroponitrile.

[b] Based on hydratroponitrile consumed. Some unchanged nitrile was recovered.

[c] Commercial sodamide was used (Farchan Research Laboratories).

[d] Necessary to heat distillation head with a flame as material tended to solidify.

[e] Sodium hydride was used as the condensing agent instead of sodamide.

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(1) This paper is abstracted from the M. S. Thesis of R. L. Jacobs, Michigan State University, June, 1955.

(2) Hauser and Brasen, *J. Am. Chem. Soc.*, **78**, 82, 494 (1956).

(3) Goerner and Workman, *J. Org. Chem.*, **19**, 37 (1954).

(4) Tilford, Van Campen, and Shelton, *J. Am. Chem. Soc.*, **69**, 2902 (1947).

(5) Tilford, Doerle, Van Campen, and Shelton, *J. Am. Chem. Soc.*, **71**, 1705 (1949).

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

Little or no unchanged hydratroponitrile was recovered from the individual alkylation reactions, except for those runs involving *n*-amyl iodide, *tert*-amyl chloride, and one run with 2-chloropentane. The distillation residue amounted to about one gram in all cases. Alkenes were sought in the alkylations with 2- and 3-chloropentane and *tert*-amyl chloride. Only the *tert*-amyl chloride was dehydrohalogenated to the alkenes. The failure to obtain more than a trace of product from the alkylation with *tert*-amyl chloride was anticipated because of previous experience and the reports of others.[4,5]

In the prior paper[3] this failure was attributed to one or more of the following: (a) a lowered reaction temperature; (b) steric hindrance or (c) dehydrohalogenation by bases. In the present work this failure is not due to a lowered reaction temperature since all the alkylations reported herein were carried out at 95 to 105°. The isolation of appreciable amounts of alkenes possessing boiling points and refractive indices corresponding to both 2-methyl-1-butene and 2-methyl-2-butene shows that the dehydrohalogenation of *tert*-amyl chloride is favored over the alkylation reaction. In one effort to avoid this dehydrohalogenation effect of the amide ion (from sodamide) on *tert*-amyl chloride, sodium hydride was substituted for sodamide since sodium hydride does *not* react with alkyl halides.[7] Again alkenes were obtained. This demonstrates that the anion from hydratroponitrile is effective in the dehydrohalogenation of the *tert*-amyl chloride. Steric factors undoubtedly aid this dehydrohalogenation by preventing the bulky anion from approaching the *tert*-amyl chloride from the rear and displacing the chloride ion.

The physical properties of the nitriles prepared in this work are listed in Table II and the derivatives prepared from them are shown in Table III. Several attempts to convert the nitriles to amides by heating them with sulfuric acid of varying strengths were unsuccessful and this method of derivatization was abandoned. It was found possible to hydrolyze nitriles I, II, III, and VI (see Table II) with potassium hydroxide in ethylene glycol or butylene glycol at 200° and to convert the acids thus obtained (without isolation) directly into the corresponding anilides. Nitriles IV and V were not attacked under the conditions described above. Even when they were heated at 210° for 24 hours with butylene glycol and potassium hydroxide, only a slight trace of presumed anilide could be isolated although the flask was badly etched. These nitriles were smoothly reduced to the corresponding amines with lithium aluminum hydride according to the procedure of Amundsen and Nelson.[8]

The difficulty observed in the hydrolysis of these alkylated hydratroponiles is similar to that reported previously.[3] Hydratroponitrile, with an α-hydrogen and an α-methyl group, is easily hydrolyzed to the amide. When the α-hydrogen is replaced by an alkyl group, the resulting nitrile can no longer be hydrolyzed to the amide. With branching on the β-carbon, the nitrile cannot be hydrolyzed to the acid under even the most drastic conditions. The *rule of six or six-number* concept of Newman[9]

TABLE II

PHYSICAL PROPERTIES OF ALKYLATED HYDRATROPONITRILES

No.	Compound	B. P., °C.	mm.	n_D^{25}	d_4^{25}	N[a]
I	2-Phenyl-2-methylheptanenitrile[b]	108	1	1.4941	0.9281	7.22
II	2-Phenyl-2,5-dimethylhexanenitrile[b]	104	1	1.4939	0.9264	7.19
III	2-Phenyl-2,4-dimethylhexanenitrile	98–99	*ca.* 1	1.4969	0.9341	6.99
IV	2-Phenyl-2,3-dimethylhexanenitrile	98–101	1	1.5013	0.9421	7.06
V	2-Phenyl-2-methyl-3-ethylpentanenitrile	105–108	1	1.5042	0.9489	7.17
VI	2-Phenyl-2-cyclopentylpropanenitrile[b]	112	1	1.5232	1.0010	7.31[c]

[a] Calculated for $C_{14}H_{19}N$: N, 6.96.
[b] Physical properties were determined on redistilled samples.
[c] Calculated for $C_{14}H_{17}N$: N, 7.03.

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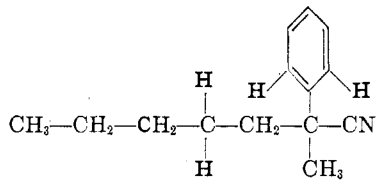
(7) Cristol, Ragsdale, and Meek, *J. Am. Chem. Soc.*, **71**, 1863 (1949).

(8) Amundsen and Nelson, *J. Am. Chem. Soc.*, **73**, 242 (1951).

(9) Newman, *J. Am. Chem. Soc.*, **72**, 4783 (1950). This paper presents data on the acid-catalyzed esterification of carboxylic acids as the basis for the *six-number* concept and extends the concept to reactions involving addition to unsaturated functions in general. Nitriles and their hydrolysis are not mentioned. The term *effective six-number* has been defined as "the number of atoms in the six position capable of yielding a coiled structure." Newman discussed the *six-number* concept thoroughly in a lecture before the Michigan State University Section of the American Chemical Society. In non-cyclic compounds



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the *six-number* is found by counting the number of atoms which are the sixth atoms removed (either carbon or hydrogen) from the more distant double or triple bonded atom (in this case nitrogen). The carbon atoms in the six position

TABLE III

DERIVATIVES OF ALKYLATED HYDRATROPONITRILES

Nitrile	Derivative	Formula	M.p., °C.	N Calc'd	N Found
I	Anilide of 2-phenyl-2-methylheptanoic acid	$C_{20}H_{25}NO$	99.5–100.5	4.74	5.04
II	Anilide of 2-phenyl-2,5-dimethylhexanoic acid	$C_{20}H_{25}NO$	110–111[a]	4.74	4.88
III	Anilide of 2-phenyl-2,4-dimethylhexanoic acid	$C_{20}H_{25}NO$	110–111[a]	4.74	4.64
IV	1-Amino-2-phenyl-2,3-dimethylhexane (VII)	$C_{14}H_{23}N$	136–139 (7 mm.)[b]	6.82	6.50
	Picrate of VII	$C_{20}H_{26}N_4O_7$	196–197[c]	12.90	13.02
V	1-Amino-2-phenyl-2-methyl-3-ethylpentane (VIII)	$C_{14}H_{23}N$	169–171 (36 mm.)[d]	6.82	6.73
	Picrate of VIII	$C_{20}H_{26}N_4O_7$	176–178[e]	12.90	12.87
	Phenylthiourea of VIII	$C_{21}H_{28}N_2S$	149–150	8.23	8.34[f]
VI	Anilide of 2-phenyl-2-cyclopentylpropanoic acid	$C_{20}H_{23}NO$	108.5–109.5	4.77	4.98

[a] A mixture of the 2,4- and 2.5-dimethyl isomers melted at 97–99°. [b] Boiling point of liquid amines; n_{D}^{25} 1.5149. [c] Yellow platelets from aqueous alcohol. [d] Boiling point of liquid amine; n_{D}^{25} 1.5170. [e] Yellow needles from aqueous alcohol. [f] *Anal.* Calc'd: S, 9.42; found, 9.31.

was used previously[3] to correlate in a semi-quantitative manner the steric relationship of alkylated hydratroponitriles and their difficulty of hydrolysis. Nitriles with an *effective six-number* of 8 or greater could not be hydrolyzed, whereas those with a *six-number* of 5 or less could be hydrolyzed. The results of this investigation are in agreement with the above observations since nitriles I, II, III, and VI with *effective six-numbers* of 5, 5, 5, and 6 respectively could be hydrolyzed whereas nitriles IV and V with an *effective six-number* of 8 failed to undergo hydrolysis.

Since 2-chloropentane and 3-chloropentane are readily converted into one another,[10] precautions were taken in their preparation to avoid this interconversion by using the pyridine-thionyl chloride procedure of Whitmore and Karnatz.[11] Although the physical constants of these chloropentanes did not agree exactly with those selected by Huntress,[10] the nitriles prepared from them (Table II) had different refractive indices, possessed certain differences in the infrared absorption spectra in the 900 to 1500 cm.$^{-1}$ region, and upon reduction produced amines which had different physical and chemical properties. Furthermore, the alkylation of hydratroponitrile with 2-chloropentane and with 2-bromopentane produced only one product. It appears, therefore, that the 2-chloropentane and 3-chloropentane samples were not mixtures.

EXPERIMENTAL[12]

Hydratroponitrile. The nitrile was prepared from hydratropic aldehyde (purchased from Van Amerigen-Haebler Inc.) *via* the oxime by the procedure of Newman and Closson.[13] The nitrile distilled at 114–116° (19 mm.), n_{D}^{20} 1.5120, n_{D}^{25} 1.5090; reported b.p. 107–110° (11 mm.),[13] n_{D}^{25} 1.5095.[2]

Sodamide was prepared as described previously.[3] Two condensations were carried out with powdered sodamide purchased from Farchan Research Laboratories.

2-Chloropentane. 2-Pentanol was prepared from *n*-propyl chloride (2 moles) and acetaldehyde (1.75 moles) *via* the Grignard reagent by a modification of the procedure of Wood and Scarf.[14] After hydrolysis of the reaction mixture and removal of the ether, the mixture was fractionated at atmospheric pressure through a 3 × 40 cm. column packed with $^3/_{16}$ in. glass helices. The 2-pentanol was collected at 114–116° (741.5 mm.), n_{D}^{20} 1.4062; reported[15] b.p. 117–118.5° (760 mm.) and n_{D}^{20} 1.4063–1.4067. Three runs gave yields of 57%, 75%, and 82%.

2-Pentanol (64 g., 0.73 mole) was converted to 2-chloropentane by the thionyl chloride-pyridine procedure of Whitmore and Karnatz[11] using Matheson-Coleman-Bell thionyl chloride. (A purified practical grade of thionyl chloride failed to yield any 2-chloropentane.) After the chloride was washed and dried, it was subjected to a preliminary distillation from a Wurtz flask. The distillate was redistilled through a 2 × 20 cm. column packed with $^3/_{16}$ in. glass helices. The 2-chloropentane, obtained in yields of 38 and 42%, distilled at 94–95° (747.5 mm.), n_{D}^{20} 1.4062; reported[11] b.p. 96.8° (760 mm.), n_{D}^{20} 1.4069.

3-Chloropentane. 3-Pentanone (172 g., 2 moles, Eastman White label grade) together with 6 g. of a copper chromium oxide catalyst,[16] was placed in a 1-l. steel bomb. Hydrogenation was carried out at 150° under an initial hydrogen pressure of 1550 p.s.i. for 4 hours. The 3-pentanol, obtained in 95% yield, was distilled through the 3 × 40 cm. helix packed column. It boiled at 111–111.5° (740 mm.), n_{D}^{25} 1.4080; reported[17] b.p. 115.5° (754 mm.), n_{D}^{25} 1.4077.

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in a benzene ring are not free, but are held rigidly in the ring and cannot shield the cyano group. They are not counted. Only one of the two hydrogen atoms on the benzene ring can be completely effective at any one time. Newman used the term *effective six-number* in discussing such cyclic compounds. For nitrile I the atoms which are counted as *six atoms* are shown in bold-face type; the effective six-number is 5. Similar considerations were used to assign an *effective six-number* of 6 to nitrile VI.

(10) Huntress, *Organic Chlorine Compounds*, John Wiley and Sons, Inc., New York, 1948, p. 1024.

(11) Whitmore and Karnatz, *J. Am. Chem. Soc.*, **60**, 2536 (1938).

(12) Melting points and boiling points are uncorrected. All analyses were by Micro-Tech Laboratories, Skokie, Ill.

(13) Newman and Closson, *J. Am. Chem. Soc.*, **66**, 1553 (1944).

(14) Wood and Scarf, *J. Soc. Chem. Ind.* (*London*), **42**, 13T (1923).

(15) Kharasch, Walling and Mayo, *J. Am. Chem. Soc.*, 61, 1560 (1939).

(16) Adkins, *Reactions of Hydrogen*, University of Wisconsin Press, Madison, Wisconsin, 1937, p. 12.

(17) Heilbron, *Dictionary of Organic Compounds*, Revised Edition, Oxford University Press, New York, 1953.

3-Pentanol was converted to 3-chloropentane in 36 to 45% yield by the thionyl chloride-pyridine method described above. It distilled at 95-95.5° (736 mm.), n_D^{20} 1.4099; reported[11] b.p. 97.8° (760 mm.), n_D^{20} 1.4104.

1-Chloro-2-methylbutane. 2-Methyl-1-butanol was prepared by adding solid trioxymethylene (70 g., 2.33 moles, dried in a desiccator over sulfuric acid) to the Grignard reagent from *sec*-butyl bromide (325 g., 2.37 moles) and magnesium (57 g., 2.37 moles) according to the procedure of Hickinbottom.[18] Fractionation through the 3 × 40 cm. column gave 125 g. (1.44 moles) or 61% of the alcohol, b.p. 123–125° (745 mm.), n_D^{20} 1.4101; reported[19] b.p. 128–129° (760 mm.), n_D^{20} 1.4111.

1-Chloro-2-methylbutane was obtained from the alcohol by the thionyl chloride-pyridine method as described. It was obtained in yields of 56 and 66%, b.p. 97.5° (735.5 mm.), n_D^{20} 1.4125; reported[20] b.p. 99.5° (750 mm.), n_D^{20} 1.4126.

Chlorocyclopentane. Redistilled cyclopentanone (b.p. 125°, 740 mm.) was reduced catalytically over a copper chromium oxide catalyst as described in the preparation of 3-pentanol. The cyclopentanol was obtained in 91% yield, b.p. 135.5° (738 mm.), n_D^{20} 1.4524; reported[21] b.p. 139–141°, n_D^{20} 1.4530. Chlorocyclopentane was obtained in about 60% yield from the cyclopentanol, concentrated hydrochloric acid, and calcium chloride as described by Yarnall and Wallis.[22] It distilled mostly at 118–122° (739 mm.), n_D^{20} 1.4510; reported b.p. 113.5–114.5°,[22] n_D^{20} 1.4510.[17]

Alkylation of hydratroponitrile. All alkylations were carried out using the high temperature procedure of Ziegler and Ohlinger[6] *exactly* as described previously.[3] The same number of moles of reactants were used as before and the reaction mixture was worked up similarly and distilled through identical equipment. In a typical run using 33 g. (0.25 mole) hydratroponitrile, 32 g. (0.3 mole) of 1-chloro-2-methyl butane, and 12–13 g. of sodamide, the following fractions were collected at 1 mm. pressure: *Fraction 1,* 1.5 g., b.p. 59–91°, n_D^{25} 1.4910; *Fraction 2,* 2.3 g., b.p. 91–98°, n_D^{25} 1.4966; *Fraction 3,* which is nitrile III, 45.3 g., b.p. 97–100°, n_D^{25} 1.4969; *Fraction 4,* 1.2 g. b.p. 99-83°, n_D^{25} 1.4970; *residue,* 1 g. The refractive index was determined frequently on small samples of product.

Derivatives. Anilides. Nitriles I, II, III, and VI were hydrolyzed and converted to the anilides as follows: The nitrile (3 g.) was added to a solution of 2 g. of potassium hydroxide in 10 ml. of ethylene glycol in a flask equipped with an air condenser. After heating the mixture in an oil bath at 200° until the evolution of ammonia ceased, the contents of the flask was poured into 75 ml. of water. Unreacted nitrile was removed by ether extraction. The aqueous solution was heated to drive off any ether and then was acidified. All attempts to isolate a solid acid at this point were unsuccessful. The acid solution was extracted with benzene, the benzene was evaporated, and the resulting liquid was refluxed briefly with thionyl chloride. The excess thionyl chloride was distilled and the last traces were purged with benzene. The resulting acid chloride was added to a solution of aniline in benzene. The benzene solution was extracted with dilute hydrochloric acid, dilute sodium hydroxide solution, and water. Evaporation of the benzene left a brown solid, which was recrystallized from aqueous ethanol (Norit). The resulting colorless solution deposited fine white needles of the anilide upon cooling.

Amines. Nitriles IV and V were reduced to the amines as follows:[8] The nitrile (10 g.) in 30 ml. of anhydrous ether was dropped slowly into a slurry of 4 g. of lithium aluminum hydride in 100 ml. of anhydrous ether. The solution was refluxed for an hour. The excess hydride was decomposed by adding dropwise in order, 4 ml. of water, 3 ml. of 20% sodium hydroxide, and 14 ml. of water. The ethereal solution was decanted and the solid aluminum hydroxide was rinsed with ether. After removal of the ether, the residual oil was subjected to a short path distillation at reduced pressure. The physical properties of amines VII and VIII, which were obtained in 92 and 87% yield, respectively, are shown in Table III. These amines failed to form crystalline acetamides, benzamides, or benzenesulfonamides. The melting points of their picrates and of the phenylthiourea of VIII are also listed in Table III.

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(18) Hickinbottom, *Reactions of Organic Compounds,* 2nd Edition, Longmans, Green and Co., New York, 1948, p. 177.

(19) Whitmore and Olewine, *J. Am. Chem. Soc.,* **60,** 2569 (1938).

(20) Brown and Groot, *J. Am. Chem. Soc.,* **64,** 2563 (1942).

(21) Noller and Adams, *J. Am. Chem. Soc.,* **48,** 1084 (1926).

(22) Yarnall and Wallis, *J. Org. Chem.,* **4,** 287 (1939).