9-Acetophenanthreneazine.—A solution containing 10 g. of 9-acetophenanthrene[6] in 10 ml. of ethanol and 3 ml. of acetic acid was heated to boiling. Hydrazine hydrate (1.8 ml.) in 3 ml. of ethanol was added slowly and the mixture refluxed for a half-hour. On cooling, a tacky material separated, but on reheating, this material crystallized yielding 8.2 g. (83%) of a yellow pulpy solid, m. p. 139–149°. Recrystallization from chloroform gave 3.9 g. (39%), m. p. 149–150°. The analytical sample was pale yellow, m. p. 149.5–150°.

Anal. Calcd. for $C_{32}H_{24}N_2$: C, 88.04; H, 5.54. Found[7]: C, 88.28; H, 5.25.

9-(Phenanthryl)-ethylcarbinol (I, R = C_2H_5).—To a solution of 9-phenanthrylmagnesium bromide,[4] prepared from 13 g. of 9-bromophenanthrene, a solution of 3 g. of propionaldehyde in 10 ml. of dry benzene was added dropwise. The reaction mixture was kept cold for two and one-half hours and then stirred at room temperature for three hours. Worked up in the usual way, the carbinol crystallized from benzene as fine white needles, 7.1 g. (79%), m. p. 102–103°. The same melting point was observed for an analytical sample obtained by repeated recrystallization.

Anal. Calcd. for $C_{17}H_{16}O$: C, 86.40; H, 6.83. Found[8]: C, 86.23; H, 6.56.

1-Bromo-1-(9-phenanthryl)-propane (II, R = C_2H_5) was prepared by the same procedure used in the preparation of the homolog (II, R = CH_3). From 24 g. of the carbinol above, 23.7 g. (78%) of crystallized material, m. p. 62–68° was obtained. In recrystallizing the product from ligroin (60–90°) care must be exercised to prevent heating the solution too long. The purest product obtained was gotten by saturating ligroin at room temperature and allowing spontaneous evaporation to occur until the product started to crystallize. In this way, a sample m. p. 69–70° was obtained as white needles which darkened on standing. Even this material was not analytically pure since it gave a high value for carbon.

3,4-Bis-(9-phenanthryl)-hexane (III, R = C_2H_5).—A mixture of 0.6 g. of magnesium, a crystal of iodine and 30 ml. of dry ether was heated for ten minutes and then a solution of 13 g. of the halide above (II, R = C_2H_5) in 30 ml. of benzene was added with stirring over the period of one hour. The mixture was refluxed for twenty hours, decomposed in the usual way, and the organic layer separated, washed and dried. Upon concentration of the solvent 4 g. of crystals, m. p. 210–223°, was obtained. By repeated fractional recrystallization from chloroform-ethanol, this was separated into a less soluble material (unidentified), which, on analysis, did not appear to be a hydrocarbon, and a more soluble material, m. p. 241–241.5°, which was obtained as white rectangular plates having approximately the expected composition.

Anal. Calcd. for $C_{34}H_{30}$: C, 93.10; H, 6.90. Found[8]: C, 92.77; H, 7.11.

2,3-Bis-(9-phenanthryl)-butandiol-2,3 by Reduction of 9-Acetophenanthrene.—(a) In basic solution: To a solution of 5 g. of potassium hydroxide in 50 ml. of 80% ethanol, 0.5 g. of 9-acetophenanthrene and 2 g. of powdered zinc were added. The mixture was refluxed with stirring for one week during which time 1 g. of powdered zinc was added daily for the first three days and once again after two more days. The solid product was collected and the zinc removed by the action of hydrochloric acid. The residue was dissolved in chloroform, filtered and allowed to crystallize. The white crystals weighed 0.2 g. (40%), m. p. 292.5–293.5°. An analytical sample was prepared by repeated recrystallization from chloroform, m. p. 294–296°.

(b) In acid solution: A solution of 2 g. of 9-acetophenanthrene in 35 ml. of ethanol was diluted with 5 ml. of water and 5 ml. of acetic acid. The mixture was stirred on the steam-bath while 5.6 g. of granulated zinc was added in small portions. The mixture was refluxed, 2 ml. of acetic acid being added every twelve hours for the first two days and one ml. of acetic acid added every twelve hours for six days thereafter. The material was treated with hydrochloric acid, dissolved in chloroform, filtered and allowed to crystallize; yield 0.2 g., m. p. 291–292°.

Anal. Calcd. for $C_{37}H_{26}O_2$: C, 86.85; H, 5.92; molecular weight, 443. Found[8]: C, 86.48; H, 6.18; molecular weight, 447 (ebulliometric, chloroform).

The pinacol was unaffected when treated with hydrogen at 1500 lb./sq. in. at 157–163° in the presence of copper chromite. It was recovered unchanged after refluxing for three hours with either acetyl chloride or acetic anhydride.

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[6] Bachmann and Boatner, THIS JOURNAL, **58**, 2098 (1936).

[7] Analysis by Micro-Tech Laboratories.

[8] Analysis by Clark Microanalytical Laboratory.

Reaction of Phenylmagnesium Bromide with Basically Substituted Nitriles

BY DAVID E. CLARK[1] AND HARRY S. MOSHER

The recent publication by Hauser, *et al.*,[2] on the reaction of γ-diethylaminobutyronitrile with various aryl Grignard reagents to give γ-diethylaminopropyl aryl ketones has prompted the report of the following related work at this time. In the course of other investigations, it was necessary to synthesize γ-, δ- and ε-piperidinoalkyl phenyl ketones. These compounds were prepared in satisfactory yields by the reaction of phenylmagnesium bromide with the corresponding basic nitrile. Such nitriles were readily obtained from the α,ω-dihalogen alkanes by conversion to the halonitriles with potassium cyanide, followed by substitution of the remaining halogen atom with the basic group.[3,4,5,6]

The preparation of γ-piperidinobutyrophenone has been previously reported by Petit[7]; however, in a review of this work, we found that hydrolysis with dilute hydrochloric acid of the reaction complex formed from phenylmagnesium chloride and γ-piperidinobutyronitrile gave rise to a white precipitate, which could be recrystallized from methyl alcohol, m. p. 214–220°. This phenomenon was not reported by Petit, since he hydrolyzed the complex with water and immediately rendered the solution basic. The formation of this solid was unexpected, since the basic ketone should have been soluble in the acid solution. A Volhard determination gave a value

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[1] Taken in part from the thesis presented to Stanford University, August, 1948, by David E. Clark in partial fulfillment of the requirements for the M.S. degree.

[2] Humphlett, Weiss and Hauser, THIS JOURNAL, **70**, 4020 (1948).

[3] Utermohlen and Hamilton, *ibid.*, **63**, 156 (1941).

[4] Strukov, *Khim. Farm. Prom.*, 332 (1933); *Chem. Abst.*, **28**, 3714 (1934).

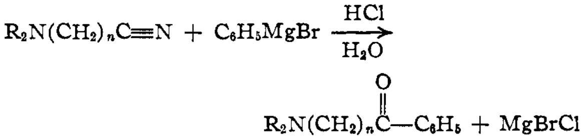
[5] Whitmore, Mosher, *et al.*, THIS JOURNAL, **66**, 730 (1944).

[6] This is the reverse of the sequence employed in ref. 2 and leads to slightly better yields in the case of the trimethylene derivatives. See ref. 5 for an improvement of the "Organic Syntheses" preparation of γ-chlorobutyronitrile.

[7] F. Petit, *Bull. sci. acad. roy. Belg., Classe de sci.*, **12**, 775 (1926).

of 14.83% chloride. This does not correspond to the hydrochloride derivative of the expected ketone, γ-piperidinobutyrophenone (13.24%), or to the dihydrochloride of the ketimine (23.38%). However, the free basic ketone could be obtained by treating this solid with 6 *N* sodium hydroxide in the presence of ether. The hydrochloride derivative prepared from the purified base melts at 180°. A similar phenomenon was also noted in the preparation of higher homologs.

By the preparation of δ-piperidinovalerophenone, and ε-piperidinocaprophenone, it is now evident that the reaction



$$R_2N(CH_2)_nC{\equiv}N + C_6H_5MgBr \xrightarrow[H_2O]{HCl} R_2N(CH_2)_n\overset{\overset{O}{\|}}{C}{-}C_6H_5 + MgBrCl$$

is general when "*n*" is equal to or more than three. It has already been shown by Bruylants[8] that anomalous reactions may occur when "*n*" is one. We have attempted several reactions when "*n*" is two, but only polymers were isolated confirming the previous report of Bruylants.[9]

Experimental

γ-Diethylaminobutyronitrile.—This was made as previously described[5] with the exception that 0.05 mole per cent. of sodium iodide was added as catalyst. This facilitated the reaction and raised the yield to 88.1%. When γ-bromobutyronitrile[10] was refluxed with excess diethylamine under these same conditions a 96.7% yield of γ-diethylaminobutyronitrile was obtained.

δ-Piperidinovaleronitrile.—This was prepared from δ-chlorovaleronitrile[11] and piperidine as described for the next lower homolog[5] and had the following properties: b. p. 107° (3 mm.), n^{20}_D 1.4659, hydrochloride derivative m. p. 150–151°.

ε-Piperidinocapronitrile.—This was prepared from ε-bromocapronitrile[12] in an analogous manner: b. p. 122° (3 mm.), n^{20}_D 1.4666, hydrochloride derivative m. p. 124°.

Preparation of γ-Piperidinobutyrophenone.—To 12 g. (0.5 mole) of magnesium turnings, 50 ml. of dry ether, and a small crystal of iodine, was slowly added 85 g. (0.54 mole) of bromobenzene dissolved in 100 ml. of ether. To the reagent thus prepared was added 38.0 g. (0.25 mole) of γ-piperidinobutyronitrile[5] dissolved in an equal volume of ether, and the reaction mixture was allowed to stand overnight. The reaction was hydrolyzed by pouring onto a mixture of 400 ml. of 6 *N* hydrochloric acid and 200 g. of ice. The white precipitate formed was filtered and treated with 6 *N* sodium hydroxide in the presence of ether. Distillation of the residue from the ether extract through a Claisen flask gave 21.0 g. of γ-piperidinobutyrophenone, b. p. 144–146° at 3 mm., n^{20}_D 1.5348, in 64.1% yield. A Volhard chloride determination on the hydrochloride derivative (m. p. 180°) showed 13.12% chlorine; calculated 13.24%.

Preparation of δ-Piperidinovalerophenone.—In an identical manner, δ-piperidinovalerophenone was prepared in 50% yield; b. p. 167° at 3 mm., n^{25}_D 1.5289. An equivalent weight determination obtained by titration with hydrochloric acid using methyl orange indicator gave a value of 245.1; calculated, 245.2. A Volhard chloride determination on the hydrochloride derivative (m. p. 170–172°) showed 12.49% chloride; calculated, 12.59%.

Preparation of ε-Piperidinocaprophenone.—Acid hydrolysis of the reaction mixture in this case gave only small quantities of a white crystalline precipitate. The solution was made strongly basic, extracted with three portions of ether, and the extracts distilled to give ε-piperidinocaprophenone (b. p. 158–160° at 0.4 mm., n^{20}_D 1.5280) in 55.6% yield. A satisfactory equivalent weight could not be obtained upon titration with acid, however, a Volhard chloride determination on the hydrochloride (m. p. 146–148°) gave a value of 12.02% chlorine; calculated, 11.98%.

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[8] Bruylants, *et al.*, *Bull. sci. acad. roy. Belg.*, **10**, 126 (1924); **11**, 261, 301 (1925); *Bull. sci. chim. Belg.*, **33**, 467 (1924); **33**, 483 (1924).

[9] Bruylants, *Bull. soc. chim. Belg.*, **32**, 266 (1923).

[10] Obtained by carefully fractionating the reaction product from trimethylene chlorobromide and potassium cyanide (Allen, *Organic Syntheses*, Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 156).

[11] Starr and Hixon, THIS JOURNAL, **56**, 1595 (1934).

[12] Trunel, *Compt. rend.*, **197**, 453 (1933).

The Synthesis of Bis-(dialkylaminoalkyl) Esters of 5-Methoxyisophthalic Acid[1,2]

BY J. C. CALANDRA AND J. J. SVARZ

It has been found that basic-alkyl esters of 4-methoxy-[3] and 4-fluoroisophthalic acid[4] exhibit local anesthetic activity. This work is a continuation of earlier studies and deals with the synthesis of the basic-alkyl esters of 5-methoxyisophthalic acid. The results of the pharmacological studies will be presented elsewhere.

Experimental

5-Methoxy-1,3-dimethylbenzene.—A commercial sample of 5-hydroxy-1,3-dimethylbenzene was purified by fractional distillation and the methyl ether was prepared according to the method of Ullmann.[5] The yield was 88%; b. p. 113–114° (50 mm.) and 192–194° at atmospheric pressure; d^{25}_{25} 0.9580, n^{25}_D 1.5105.

5-Methoxyisophthalic Acid.—This compound was prepared using the method described by Fosdick and Fancher.[3] The acid was obtained as a white solid in a 54.3% yield, m. p. 267–268°. *Neut. equiv.* Calcd. for $C_9H_8O_5$: 98.03. Found: 98.50.

5-Methoxyisophthalyl Chloride.[3]—This compound was obtained in 75.5% yield, m. p. 48–49°. *Anal.* Calcd. for $C_9H_6O_3Cl_2$: Cl, 30.12. Found: Cl, 29.97.

Dimethyl 5-Ethoxyisophthalate.[3]—This compound recrystallized from methanol was prepared in 92% yield, m. p. 110.5–111°. *Anal.* Calcd. for $C_{11}H_{12}O_5$: C, 58.92; H, 5.40. Found: C, 58.94; H, 5.41.

Bis-(dialkylaminoalkyl)-5-methoxyisophthalate Di-hydrochloride.—These esters were prepared using the method mentioned above[3] with a slight modification in that two moles of the aminoalkanols were treated with one mole of the acid chloride in the absence of a solvent. All of these compounds possess local anesthetic activity. The analytical data are presented in Table I.

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[1] Presented before the Division of Medicinal Chemistry at the 110th meeting of the American Chemical Society at Chicago, Illinois, September 12, 1946.

[2] From the Master of Science thesis of J. J. Svarz.

[3] L. S. Fosdick and O. E. Fancher, THIS JOURNAL, **63**, 1277 (1941).

[4] L. S. Fosdick and J. C. Calandra, *ibid.*, **65**, 2308 (1943).

[5] F. Ullmann, *Ann.*, **327**, 104 (1903).