1-ethyl-4-(β-dimethylaminoethylamino)-piperidine (IV) in 500 ml. of xylene, 40.2 g. (0.291 mole) of potassium carbonate and 0.5 g. of copper powder was added 49.8 g. (0.291 mole) of benzyl bromide during thirty minutes. The suspension was stirred then for forty hours at 160 ± 10°. The mixture was worked up as above to give, in addition to 27 g. of a water and ether-insoluble oil, a fraction which boiled mainly at 185–188° (0.7 mm.) and solidified in the receiver. Attempts to obtain an analytically pure sample of this compound which recrystallized from ether, m. p. 99–100°, or of its hygroscopic hydrochloride were unsuccessful. The picrate prepared in ethanol was only very slightly soluble in ethanol or acetic acid but could be recrystallized from ethyl acetate. The tripicrate, m. p. 193–195° (dec.), was prepared in ethanol and recrystallized from ethyl acetate.

Pyrrolidylacetonitrile.—A solution of 208 g. (2.0 moles) of sodium bisulfite in 200 ml. of water was added to 142 g. (2.0 moles) of pyrrolidine at 25°. Then 162 g. (2.0 moles) of 37% aqueous formaldehyde was added with stirring and cooling below 30°. The temperature was raised to 60°, and 130 g. (2.0 moles) of potassium cyanide in 200 ml. of water was added with stirring during one-half to three-quarters hours. The milky solution was stirred at steam-bath temperature for six hours. After the solution was cooled the liquid was decanted and the wet organic layer of about 210 g. was separated. The aqueous layer was extracted four times with 200 ml. portions of ether and the combined organic layers dried over magnesium sulfate. By distillation 170.7 g. (77%) of pyrrolidylacetonitrile, b. p. 83° (17 mm.), was obtained. Redistillation of a sample gave a product which boiled at 86° (22 mm.), $n^{22.6}D$ 1.4558. The analysis of this material varied about 0.7% from the calculated value for carbon and hydrogen. The picrate, m. p. 153–154° (dec.), prepared from it analyzed for the picrate of pyrrolidylacetonitrile after recrystallization from ethanol.

Anal. Calcd. for $C_{12}H_{13}N_5O_7$: C, 42.48; H, 3.86; N, 20.65. Found: C, 42.58; H, 3.80; N, 19.87.

β-Pyrrolidylethylamine.—Pyrrolidylacetonitrile, 165 g. (1.5 moles), was shaken in a bomb under hydrogen at 85° in the presence of 10 g. of Raney nickel catalyst. After five hours 81% of the theoretical amount of hydrogen had been absorbed. The catalyst was removed by filtration and the residue was distilled at atmospheric pressure to give a forerun of 18.0 g., b. p. 158–161°, and 63.5 g. of the primary amine, b. p. 161° ± 2°. The dipicrate prepared from either fraction melted at 218–220° (dec.).[8]

Anal. Calcd. for $C_{18}H_{20}N_8O_{14}$: C, 37.77; H, 3.52; N, 19.58. Found: C, 38.02; H, 3.51; N, 18.67.

In addition to the primary amine the corresponding secondary amine, *bis*-pyrrolidylethylamine, was obtained, which upon redistillation boiled at 161° (17 mm.) and weighed 36.2 g.

Anal. Calcd. for $C_{12}H_{25}N_3$: C, 68.19; H, 11.92; N, 19.88. Found: C, 68.16; H, 11.28; N, 18.88.

Summary

1. The preparation of five 4-aminopiperidines by reductive alkylation is described.

2. The alkylation of these secondary amines with benzyl bromide or α-bromopyridine gave potential antihistamine agents.

3. 1-Ethyl-4-(N-benzyl-N-α-pyridylamino)-piperidine proved to be the most active of the compounds toward histamine induced spasms in the isolated gut.

4. An improved synthesis of pyrrolidylethylamine is given.

---

[8] Van Alphen (*Rec. trav. chim.*, **58**, 1105 (1939)) reported that pyrrolidylethylamine boiled at 166–167° and that its picrate melted at 219°.

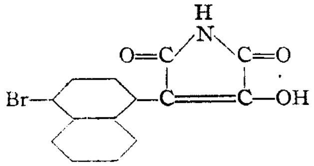
KALAMAZOO, MICHIGAN RECEIVED JUNE 21, 1948

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, UNIVERSITY OF DELAWARE]

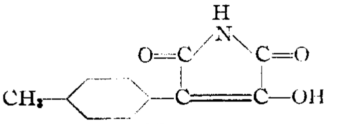
The Reaction of Bromine with Arylcyanopyruvic Esters

BY GLENN S. SKINNER, WILSON MCA. KLEIBACKER, RONALD ROSENBERG, JULES A. GLADNER AND STANLEY L. REED

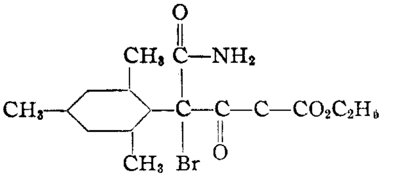
In a previous report[1] it was shown that ethyl cyanophenylpyruvate reacts with bromine to yield *p*-bromophenylhydroxymaleimide. This work has been continued with the object of determining the result of the reaction when the α-naphthyl radical is substituted for the phenyl radical and also when ortho and para positions in the benzene nucleus are blocked. Typical products obtained are represented by the formulas



I



II



III

Ethyl cyano-α-naphthylpyruvate reacts similarly to yield 4-bromo-α-naphthylhydroxymaleimide (I). The ease with which this substance is purified indicates that it is the essential product of the reaction. Its identity was established by oxidation to 4-bromo-1-naphthoic acid. This result adds weight to the idea that the bromine first adds to the enol form and then rearranges to the ring. If substitution were the first step the purification should have been complicated by the formation of isomers due to the entry of bromine also in positions 5 and 8.

Although no *o*-bromophenylhydroxymaleimide was isolated from the reaction of bromine on ethyl cyanophenylpyruvate, one might predict that the

---

(1) Skinner, Coghlan and Berlin, THIS JOURNAL, **64**, 2600 (1942).

blocking of either the ortho or para positions with a methyl group would lead to the entry of bromine in an alternative position. To obtain the needed cyanotolylpyruvates the mixture of chloromethyltoluenes resulting from the chloromethylation of toluene was employed as the starting material. If the para position in the phenyl radical is blocked by the methyl group the chief product is *p*-tolylhydroxymaleimide (II) and no evidence was obtained that bromine enters the ortho position. A methyl group in the ortho position, however, does not completely deny the entry of the bromine in the para position.

Since both ortho and para positions in ethyl cyanomesitylpyruvate are blocked by methyl groups, the bromine should in this case remain in the side chain. This result was obtained since the product is ethyl bromocarbamidomesitylpyruvate (III). This substance was identified by alkaline hydrolysis to 2,4,6-trimethylmandelic acid. It is also noteworthy that cyclization did not occur, which is comparable to the behavior of aliphatic cyanopyruvic esters.

Experimental

Products from Ethyl Cyano-α-naphthylpyruvate.—To a well-stirred solution of sodium ethoxide prepared from 11.5 g. of sodium and 165 cc. of absolute alcohol was added rapidly from a separatory funnel a mixture of 83.5 g. (0.50 mole) of α-naphthylacetonitrile and 77.4 g. (0.53 mole) of ethyl oxalate. The salt of ethyl cyano-α-naphthylcyanopyruvate began to crystallize almost at once. After standing overnight, water (100 cc.) was added to effect rapid solution of the salt. The mixture was heated to 35° and acidified strongly with hydrochloric acid while being stirred and cooled. The crude product precipitated as an oil which crystallized upon cooling in ice and weighed 139 g. Recrystallization from a mixture of equal volumes of benzene and ligroin gave 80 g. of light yellow crystals, m. p. 114–115°. *Anal.* Calcd. for $C_{16}H_{13}O_3N$: N, 5.29. Found: N, 5.32.

Thirteen and four-tenths grams (0.050 mole) of ethyl cyano-α-naphthylpyruvate was warmed with 55 cc. of dry chloroform until dissolved. After cooling to room temperature there was added with good mixing 0.9 g. of water and then 8.6 g. (0.055 mole) of dry bromine. The mixture was kept at room temperature for five minutes, then heated to 35–38° and kept at this temperature for ten minutes when crystals began to separate. The reaction was completed by heating for five hours at 55–65°. The product which separated at room temperature gave 5.5 g. of orange-colored crystals when crystallized from 60 cc. of hot alcohol, m. p. 229–230°. Another crystallization from hot absolute alcohol yielded lemon-yellow crystals, m. p. 255–256°. *Anal.* Calcd. for $C_{14}H_8O_3NBr$: N, 4.39. Found: N, 4.43.

To obtain lemon-yellow crystals it is necessary that the mother liquor be not allowed to concentrate by evaporation during the crystallization, since the crystals are orange-colored under these conditions.

The bromo-α-naphthylhydroxymaleic imide (3.2 g.) was dissolved in a solution of 1.4 g. of sodium carbonate in 50 cc. of water. To the well-stirred solution cooled in a bath of ice and water 140 cc. of a 3% solution of potassium permanganate was added in a half hour. After standing overnight at room temperature the colorless filtrate was heated to boiling and stirred while being acidified with hydrochloric acid. The bromo acid weighed 0.6 g. and melted at 216°. Recrystallization first from absolute alcohol and then from benzene gave a product melting at 216–218°. The melting points reported for 4-bromo-1-naphthoic acid vary from 216 to 220°.[2]

Products from Ethyl Cyanomesitylpyruvate.—Twenty-five and nine-tenths grams (0.100 mole) of ethyl cyanomesitylpyruvate[3] was dissolved in 80 cc. of chloroform contained in a 200-cc. flask connected to a condenser by a glass joint and similarly provided with two small dropping funnels. Five and three-tenths cc. (0.105 mole) of bromine and 1.8 cc. of water were gradually and simultaneously added to this solution with good mixing. After standing for two hours a heavy precipitate of white crystals had separated. The mixture was heated for six hours at 50° and then allowed to stand for two days. The white crystalline product after crystallization from alcohol weighed 25.7 g. (72%), m. p. 206.5–207.5°.

Anal. Calcd. for $C_{15}H_{18}O_4NBr$: N, 3.93. Found: N, 4.07.

A solution of 8.4 g. of potassium hydroxide in 15 cc. of water was added to a solution of ethyl bromocarbamidomesitylpyruvate in 30 cc. of alcohol. After refluxing for six hours the solution was diluted with twice its volume of cold water. Acidification of the filtered solution gave 4.8 g. of 1,3,5-trimethylmandelic acid, m. p. 147–148°.

Products from Ethyl Cyanotolylpyruvates.—The starting mixture of chloromethyltoluenes was made by passing hydrogen chloride into a mechanically stirred mixture of 138 g. of toluene, 138 g. of formalin and 475 g. of hydrochloric acid (1.19) for sixteen hours at 60–70°; yield 147 g. The combined product from the different preparations (1400 g.) distilled at 95–100° (17 mm.). Although partial separation was obtained by freezing from toluene solution at −80°, it was found more practical to complete the separation after formation of the cyanopyruvates. The mixed chlorides gave the nitriles in a yield of 81%, b. p. 121–126° (14 mm.) or 128–132° (17 mm.).

In a typical experiment a solution of sodium ethoxide prepared from 17.1 g. of sodium and 250 cc. of absolute alcohol was allowed to cool until crystallization began and then quickly mixed with 96.8 g. of the mixture of tolylacetonitriles and 108.5 g. of ethyl oxalate. After standing overnight the alcohol was removed through a fractionating column under diminished pressure from a bath that was not heated above 50°. The residual mixture solidified when allowed to stand for twenty-four hours longer. Ether (50 cc.), 400 g. of finely crushed ice, and 100 cc. of ice-cold water were added, and the contents were agitated very briefly to partially dissolve the caked material. Eighty-five cc. of hydrochloric acid (1.19) was added immediately and the flask was shaken until the solid was disintegrated. After mixing with 75 cc. of petroleum ether the product was triturated under suction on a large Buchner funnel and kept covered with crushed ice while it was washed with ice-cold water and a mixture (2:3) of ether and petroleum ether. The yield of crystalline product was 88–91%, m. p. 70–80°. Very poor yields of crystalline product were obtained when the reaction was not carried to completion in the above manner.

The mixture of tolylcyanopyruvates was dissolved in two parts by weight of hot toluene. After cooling somewhat, one-fifth to one-fourth its weight of petroleum ether was stirred in. The container was covered to prevent evaporation and allowed to stand overnight at room temperature. The fibrous crystalline product, consisting largely of the higher melting (ortho) isomer, was filtered with suction, washed with toluene–petroleum ether and then with petroleum ether. The petroleum ether was removed at atmospheric pressure and the toluene under diminished pressure in a weighed fractionating flask. The residue was dissolved in one-half its weight of hot absolute alcohol which was used in portions to effect the transfer to a small beaker. The solution was then allowed to stand at room temperature protected from evaporation. The large transparent crystals were filtered under suction with the aid of a rubber dam without washing. A second crop, which was chiefly the lower melting (para) isomer, was obtained by cooling the filtrate in an ice–salt mixture. More dilute alcohol solutions were satisfactorily crystallized by cooling in a dry

---

[2] Jacobs, *et al.*, *J. Org. Chem.*, **11**, 27 (1946); Zalkind, *Ber.*, **67B**, 1031 (1934); Gomberg and Blicke, THIS JOURNAL, **45**, 1765 (1923).

[3] "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., p. 287.

ice–acetone mixture. After removing the alcohol from the final filtrate the whole process was repeated several times. The collected higher melting fractions were recrystallized from toluene–petroleum ether and the collected lower melting fractions were recrystallized from alcohol.

Ortho isomer: m. p. 115–116°. *Anal.* Calcd. for $C_{13}H_{13}O_3N$: N, 6.06. Found: N, 6.02.

Para isomer: m. p. 89–90°. *Anal.* Calcd. for $C_{13}H_{13}O_3N$: N, 6.06. Found: N, 5.95.

The esters were hydrolyzed to the tolylacetic acids by refluxing with aqueous potassium hydroxide, and the acids were then converted to the amides. The ester (m. p. 115–116°) gave *o*-tolylacetamide (m. p. 161–163°) and the ester (m. p. 89–90°) gave *p*-tolylacetamide (m. p. 185°). One gram of the ortho amide was dissolved by refluxing with a solution of potassium hydroxide and then oxidized in the usual way with potassium permanganate. The acid after extraction with ether and crystallization from a minimum of hot water proved to be *o*-phthalic acid. This acid was also obtained directly from the higher melting ester by hydrolysis and oxidation; m. p. 208–210° (sealed tube). An authentic sample of *o*-phthalic acid melted at the same temperature under the same conditions.

o-Tolylhydroxymaleimide was prepared by passing a current of hydrogen chloride into a mixture of 23.1 g. of cyano-*o*-tolylpyruvic ester, 2.3 g. of water and 44 cc. of absolute alcohol for one hour at 70°. The yield of crude product (m. p. 183–187°) obtained by filtration and concentration of the mother liquor was 17.6 g. (87%). The recrystallized product melted at 186–187°.

Anal. Calcd. for $C_{11}H_9O_3N$: N, 6.89. Found: N, 6.98.

Bromination of 23.1 g. of ethyl cyano-*o*-tolylpyruvate according to the procedure employed for ethyl cyanophenylpyruvate gave 16.6 g. of yellow crystals, which precipitated from the chloroform, and 9.0 g. of very soluble material. The precipitate was dissolved in the minimum amount of cold alcohol, and the solution was diluted with an equal volume of water. Gradual concentration of the filtrate and recrystallization of the fractions yielded a total of 8.4 g. of the expected 4-bromo-*o*-tolylmaleimide, m. p. 237.5–238.5°.

Anal. Calcd. for $C_{11}H_8O_3NBr$: N, 4.97. Found: N, 4.93.

This imide (4.2 g.) was dissolved in 30 cc. of a 10% solution of potassium hydroxide and heated rapidly to boiling. Upon cooling, 1.5 g. of 4-bromo-*o*-tolylacetamide separated. The process of heating the filtrate was repeated twice in the same way to effect complete hydrolysis of the imide, total yield 3.2 g., m. p. 176–178°.

Anal. Calcd. for $C_9H_{10}ONBr$: N, 6.14. Found: N, 6.02.

The amide was very insoluble and was hydrolyzed by long refluxing with dilute potassium hydroxide to the acid which was oxidized by hot permanganate to 4-bromo-*o*-phthalic acid, m. p. 176–178°. This very soluble acid was isolated by extraction with ether and crystallization from water.

The remainder of the product of the reaction of bromine on cyano-*o*-tolylpyruvic ester is a mixture containing *o*-tolylmaleimide and unstable products. This material is being further investigated.

The reaction product from 23.1 g. of ethyl cyano-*p*-tolylpyruvate did not set to a solid mass and the bromine disappeared more slowly. The suspended needle-like yellow crystals were filtered and washed with cold chloroform; yield 16.5 g., m. p. 255–261°. One crystallization from absolute alcohol gave 10.4 g. of the unbrominated imide, m. p. 263–264°. This imide is much less soluble in alcohol than the imide from the ortho isomer.

Anal. Calcd. for $C_{11}H_9O_3N$: N, 6.90. Found: N, 6.87.

Summary

1. A method has been devised for the separation of a mixture of *o*- and *p*-tolylcyanopyruvates.
2. A comparison of the reactions of bromine with *o*-tolyl-, *p*-tolyl-, mesityl- and *α*-naphthylcyanopyruvates has been made.

NEWARK, DELAWARE RECEIVED JULY 6, 1948

[CONTRIBUTION FROM SOCONY-VACUUM LABORATORIES, A DIVISION OF SOCONY-VACUUM OIL CO., INC., RESEARCH AND DEVELOPMENT DEPARTMENT]

Aminomethylation of Thiophene. II. The Intermediate N-(2-Thenyl)-formaldimines and their Reactions

BY HOWARD D. HARTOUGH, SEYMOUR L. MEISEL, EMIL KOFT AND JOHN W. SCHICK

In the original article of this series[1] it was reported that 2-thenylamine, I, and di-(2-thenyl)-amine, II, were the primary reaction products of thiophene, formaldehyde and ammonium chloride.

Further investigation has led to the isolation of new intermediates, the N-(2-thenyl)-formaldiamines, which can be formed as the primary reaction products to the exclusion of I and II. The formation of these products is consistent with the previously reported basic molar ratios[1] of this reaction.

It has also been noted that the mixing of neutral solutions of formaldehyde and ammonium chloride immediately produced solutions of *p*H of about 1. The high acidity of ammonium chloride-formaldehyde solutions has been previously noted by Werner[2] who postulated the existence of formaldimine, $CH_2{=}NH$, from this observation.

These observations, in conjunction with the isolation of N-(2-thenyl)-formaldimine (2-methyleneiminomethylthiophene), III, from the reaction of formaldehyde, ammonium chloride and thiophene, now make possible a fairly accurate summation of the over-all reaction.

Equation (1) represents an equilibrium reaction and the hypothetical $CH_2{=}NH$ reacts rapidly with thiophene (2) at 65° to form IV. This in turn is quantitatively converted to V, the hydrochloride salt of III, as is represented in equation (2a). This latter step (3) has been carried out in 95% yields from authentic I to substantiate this theory. Equation (4) indicates the course of reaction, as previously reported, for the production of I and II by refluxing the reaction mixture at

---

(1) Hartough, Lukasiewicz and Murray, THIS JOURNAL, **70**, 1146 (1948).

(2) Werner, *J. Chem. Soc.*, **111**, 844 (1917).