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On the Alkylation of Diphenylpyridylmethanes

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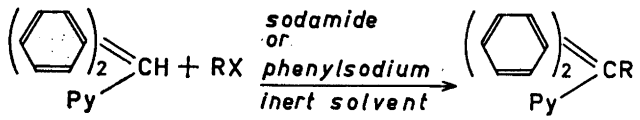
The 2-, 3-, and 4-isomers of diphenylpyridylmethane have been alkylated in an inert solvent (generally toluene) by using commercial, ground sodamide as basic agent. The diphenyl-3-pyridylmethane reacts definitely slower than the 2- and 4-isomers in forming sodium compounds when treated with sodamide in the refluxing solvent. The yields of alkylated compounds also proved to be lower in this case. Attempts to prepare the sodium compound of the 3-isomer by using sodamide in liquid ammonia or by using phenylsodium did not improve the yield of alkylation product.

The present authors have previously reported the result of their studies of the alkylation at the *a*-position of N,N-disubstituted arylacetic acid carbonamides [1] and of N,N-disubstituted toluene(*a*)sulphonamides and diphenylmethane(*a*)sulphonamides [2]. In these cases, the activation of the hydrogen atom at the *a*-position is caused by the phenyl group(s) and the carbonamide or sulphonamide group. In connection with these studies, we found it to be of interest to look somewhat at the alkylation conditions of the diphenylpyridylmethanes. The trend of this work, like the preceding ones, has been to find out the simplest, least laborious alkylation method. The reaction can be represented by the formula:



Py = 2-, 3- and 4-pyridyl. R = *neo*hexyl, *n*-octyl and *p*-chlorobenzyl. X = halogen.

It is well known, that the *a*-hydrogen of triphenylmethane is very active and can be fairly easily replaced by sodium or other alkali metals. The sodium compound, generally named tritylsodium, is, however, generally not prepared from the hydrocarbon but from trityl chloride and sodium amalgam [3,4] or, as we have found most convenient, from trityl chloride and sodium dispersion. Its preparation from the hydrocarbon requires a fairly strong basic agent, *e.g.* phenylsodium. It can presumably also be prepared from tolylsodium or diphenylmethylsodium, but since these compounds are most easily prepared *via* phenylsodium, these routes are of less interest. Of interest in this context is that tritylsodium cannot be prepared merely from sodamide and the hydro-

carbon in boiling toluene. In contrast to triphenylmethane and not quite unexpectedly, all the three diphenylpyridylmethanes form sodium compounds under this reaction condition. Metalations of diphenylpyridylmethanes have been reported earlier but, as far as we can find, not with this simple procedure. These metalations have been carried out by means of butyllithium or the phenylsodium — phenyllithium complex [5].

2-Pyridyldiphenylmethane and the 4-isomer react easily when refluxed with sodamide in toluene, giving, respectively, brick red and bright red solutions from which the sodium compounds begin to precipitate after a fairly short time of reflux. Benzene can even be used as solvent but in most cases toluene is to be preferred. The strong evolution of ammonia ceases after one or two hours reflux but the formation of sodium compound is not complete since parts of the sodamide remain enclosed in the precipitate. A second "ammonia peak" is therefore observed after the alkylating agent has been added and the precipitated sodium compound has reacted and disappeared. The sodium compounds are fairly stable and some alkylating agents such as ordinary alkyl chlorides react slowly with them even at the reflux temperature of the reaction mixture. Unless the chlorides are rather reactive, bromides are to be preferred. For further details, we refer to the experimental part.

It is obvious that at least the 2- and 4-pyridyldiphenylmethanes can be alkylated generally by this simple procedure. Of course, the groups intended to be introduced must not contain hydrogen atoms more mobile than the *a*-hydrogen atom of the parent methane, or groups which may rearrange as to form such active hydrogen. However, the reaction mixtures often are difficult to work up. When bulky groups are introduced, the alkylation product can be separated from the parent methane and some tarry products by distillation *in vacuo* but this separation method demands fairly bulky groups. Indeed, even the *neo*hexyl derivative is difficult to isolate from the parent methane by mere distillation. Moreover, in most cases the alkylation product is more soluble in most organic solvents than is the parent methane, a fact which leads to considerable losses during repeated recrystallization. Therefore, in this paper, we have selected *p*-chlorobenzyl chloride and octyl bromide as alkylating agents. We have also included the results from attempts with *neo*hexyl bromide, but the alkylation products proved to be difficult to isolate in yields which are representative of how the alkylation had proceeded.

As expected, 3-pyridyldiphenylmethane behaves somewhat differently compared with the 2- and 4-isomers. It reacts definitely slower with sodamide in boiling inert solvents than do the 2- and 4-isomers. In boiling benzene, the formation of the dark brown to almost black sodium compound proceeds very slowly and the yields of alkylation products are very low even after prolonged reflux. Toluene and xylene give better results and the yields calculated on the parent methane seem to increase to some extent with the temperature in alkylations with *n*-octyl bromide. On the other hand, the amounts of tarry remainders increase when higher temperatures are used. Yields somewhat higher than 40 % have only rarely been obtained. We have also tried to get a more complete sodium compound formation by using liquid ammonia and sodamide in this step but this procedure does not seem to give any improvement. Nor did another attempt in which phenylsodium was used as metalation agent

improve the yield. In these two last attempts, *n*-octyl bromide was used as alkylating agent.

Briefly, one can say that the difference between the diphenylpyridylmethanes on one side and triphenylmethane on the other is caused by the higher degree of electron attraction power of the pyridine nucleus compared with the phenyl nucleus (as the picolines are stronger acids than toluene). Within the diphenylpyridylmethane series, the 2- and 4-pyridyl compounds are the most active ones as is also the case within the picoline series.

Whether or not any side-reactions occur during the sodamide treatment or during the alkylation itself is difficult to decide. In addition to the alkylation product and limited amounts of the parent methane (in the case of the 3-isomer, considerable amounts), only reddish brown tarry oils or semisolid products seem to occur in the reaction mixture or seem to have been formed during the distillation. Amination of the pyridine nucleus (Chichibabin reaction) and/or metalation of the aromatic nuclei may be mentioned as examples of side-reactions which cannot be excluded as completely improbable.

EXPERIMENTAL

The diphenylpyridylmethanes used as starting materials have been prepared by the conventional route *via* the carbinols. The improved method of reduction of diphenylpyridylcarbinols recently reported in a paper by Otto *et al.*[5] has been used for the preparation of diphenyl-3-pyridylmethane but the 2- and 4-compounds had been prepared before the appearance of this paper. Since the earlier reported synthesis of diphenyl-3-pyridylcarbinol from 3-bromopyridine [6] is fairly troublesome, we have instead prepared this carbinol from the easily available 3-benzoylpyridine [7] and phenyllithium in excellent yield. Attempts to prepare the carbinol from 3-benzoylpyridine or ethyl nicotinate and phenyl magnesium bromide by the conventional procedure have given very unsatisfactory yields, As has been reported recently by Fuson and Miller [8], 3-benzoylpyridine reacts with phenylmagnesium bromide under formation of 45 % of dihydro-3-benzoyl-4-phenylpyridine and only 22 % of 3-pyridyl-diphenylcarbinol.

Diphenyl-3-pyridylcarbinol hydrochloride. A solution of phenyllithium in ether, prepared from 13.2 g (1.88 mole) of lithium, is cooled to −5°. While stirring, a solution of 140 g (0.76 mole) of 3-benzoylpyridine in 400 ml of dry ether is added by means of a dropping funnel during the course of 20−25 min. and during intermittent cooling with a dry ice-ethanol bath in order to keep the temperature at about −5°. When the addition is finished, the cooling bath is removed and the reaction mixture is left at room temperature and stirred for 1.5 h. 500 ml of 10 % hydrochloric acid is added as rapidly as possible, while cooling with the cooling bath. The temperature in the flask is kept at 20−25° during the addition of the acid. The mixture is now left at room temperature, while stirring, for about 30 min. The precipitated hydrochloride is filtered off, washed with ether and dried at room temperature. It is then washed by dispersing in 500 ml of acetone and is filtered off again, washed with ether and dried. The yield is about 225 g or approximately quantitative (calculated on 3-benzoylpyridine). The product melts at 226−229° and is sufficiently pure to be used in the reduction step.

Diphenyl-n-octyl-2-pyridylmethane. 17.2 g (0.07 mole) of diphenyl-2-pyridylmethane, 3.0 g of commercial, ground sodamide and 100 ml of dry toluene are refluxed in a flask equipped with stirrer, reflux condensor, and thermometer. A strong evolution of ammonia begins and the contents become brick red. After about one hour's reflux, a thick precipitate of the sodium compound has been formed in the flask and the ammonia evolution has almost ceased. The contents in the flask are cooled somewhat (to about 100°), and 15.5 g (theoretically 14.5 g) of *n*-octyl bromide are added dropwise by means of a dropping funnel *via* the condensor. During the course of the addition, the precipitate disappears almost completely and evolution of ammonia begins again. The dropping funnel and the condensor are rinsed with a small amount of dry toluene and the flask is heated to reflux and is maintained at this temperature for 5 h. The contents in the flask are cooled to

room temperature, water is added and the toluene layer is washed with water in a separatory funnel. The toluene layer is dried with anhydrous sodium sulphate and the toluene is driven off. The remaining reddish oil is distilled *in vacuo*. After a fore-run of a few grams, the main part distils at 185—195°/0.1 mm (20.4 g). Redistillation gives 19.5 g (77 %) of an almost colourless, viscous oil with b.p. 190—195°/0.1 mm. (Found: C 87.11; H 9.04; N 3.79. Calc. for $C_{26}H_{31}N$ (357.5): C 87.34; H 8.74; N 3.92.) Picrate: M.p. 178—179° (from alcohol).

After standing some weeks, the oil solidifies. Two recrystallizations from small amounts of petroleum ether give colourless crystals with m.p. 41—42.5°.

Diphenyl-n-octyl-4-pyridylmethane. This synthesis is carried out analogously to the preceding one. The colour of the sodium salt of the 4-isomer, however, is blood red. The final product is redistilled at 200—202°/0.1 mm. The *n*-octyl derivative is a viscous almost colourless oil. Yield 56.5 %. (Found: C 86.90; H 8.87; N 3.85.) Picrate: M.p. 139—141° (from alcohol).

Diphenyl-n-octyl-3-pyridylmethane. The sodium compound, used in the preparation of this compound, is prepared in three different ways:

a) With sodamide. A mixture of 24.5 g (0.1 mole) of diphenyl-3-pyridylmethane, 4.2 g of sodamide and 125 ml of dry toluene is refluxed for about 2 h. The ammonia evolution is fairly strong at the beginning of the reflux and the contents of the flask become intensely dark brown. The heating is interrupted and *n*-octyl bromide is added by means of a dropping funnel at about 100° until the colour of the contents lightens. About 10 g or half the total amount of bromide (20.0 g, theoret. 19.3 g), are consumed in this step. The temperature is raised and the mixture is refluxed for about half an hour. The evolution of ammonia is fairly strong immediately after the addition of the bromide. This procedure is repeated again and the remainder of the bromide added, followed by reflux for 4 h. The reaction mixture is worked up in the usual way, and the remaining oil distilled. A fore-run at 155—160°/0.2 mm consists of 14.5 g (64 %) of the parent methane. Another fraction at 185—200°/0.2—0.5 mm consists of fairly pure *n*-octyl derivative, 10.0 g (28 %). After redistillation, 7.0 g (20 %) is obtained as a viscous, colourless oil. B.p. 187—190°/0.1 mm. (Found: C 86.80; H 8.82; N 3.87.) Picrate: M.p. 117—118° (from alcohol).

The above method can be modified and xylene used as solvent: The mixture is refluxed for 2 h, cooled to about 120° and the bromide is added. After the addition of the bromide, which gives definitely exothermic reaction with decolourization of the flask contents, the temperature is increased and the mixture refluxed for 3 h. The recovered amount of parent methane is in this case 7.0 g (28 %). The yield of *n*-octyl derivative with b.p. 194—200°/0.1 mm is 15.0 g (42 %). The amount of tarry remainder in the distillation flask is definitely larger in this case than in the preceding one.

b) Sodamide in liquid ammonia. Sodamide in liquid ammonia is prepared in conventional manner from 2.7 g of sodium. 24.5 g (0.1 mole) of the methane, dissolved in 100 ml of dry toluene is added by means of a dropping funnel. The temperature is kept at about 35° by intermittent cooling of the flask. The ammonia is allowed to evaporate while the flask is flushed slowly with nitrogen. The contents are now warmed gently to 70—80°. 20.0 g (theoret. 19.3 g) of octyl bromide, diluted with 25 ml of dry toluene are added slowly, during which procedure the dark brown colour becomes pale. After the addition of the bromide, the contents are refluxed for 2 h. The reaction mixture is worked up in the usual way. Distillation gives two main fractions: the first one at 150—165°/0.1 mm consisting of 15.0 g (61 %) of parent methane; the second one at 195—200°/0.2 mm consisting of 11.0 g (31 %) of the *n*-octyl derivative.

c) With phenylsodium. Description of the metalation procedure has been given earlier [2]. The solution of 24.5 g (0.1 mole) of the methane in 50 ml of dry toluene is added to the phenylsodium suspension (from 5.0 g of sodium) while stirring at a temperature of about 30° (intermittent cooling). After the addition the stirring is continued for 15 min. The *n*-octyl bromide (20.5 g), diluted with 10 ml of dry toluene, is added drop by drop. During this procedure the dark colour becomes paler and disappears at the end of the addition. The stirring is continued for 1 h after the addition. A few ml of alcohol are added to the reaction mixture before the addition of water but, otherwise, the mixture is worked up in the usual way. At distillation, 12.5 g (15 %) of the parent methane is recovered (b.p. 165—170°/0.3—0.4 mm). The octyl derivative distils at 200—205°/0.3—0.4 mm with a yield of 13.0 g (36 %). The remainder in the distillation flask is small (2 g).

p-*Chlorobenzyl-diphenyl-2-pyridylmethane.* 22.1 g (0.09 mole) of diphenyl-2-pyridylmethane, 3.7 g of sodamide and 125 ml of dry xylene are refluxed for 3 h. The *p*-chlorobenzyl chloride (15.0 g, theoret. 14.5 g) dissolved in 50 ml of dry xylene is added during the course of 15 min. The mixture is refluxed for 2.5 h at which time the evolution of ammonia has ceased. The reaction mixture is worked up in the usual way. A main fraction (210—215°/0.1—0.2 mm) gives 16.5 g or 49.5 %. Recrystallization from a mixture of methanol and cyclohexane gives 14.8 g (44.5 %). M.p. 148—151.5°.

With toluene as solvent the yields have been lower (about 20 %), but we think that this yield may be improved. A sufficiently pure product melts at 151—152.5°. (Found: C 81.40; H 5.34; N 3.72. Calc. for $C_{25}H_{20}NCl$ (369.9): C 81.17; H 5.45; N 3.79).

p-*Chlorobenzyl-diphenyl-4-pyridylmethane* is prepared in toluene by the conventional method but the mixture is kept at a temperature of about 80° throughout the synthesis. 0.1 mole of the parent methane is used. The after-heating lasts for 9 h. The reaction mixture is worked up as above. The remaining oil, on distillation, gives two main fractions: at 160—165°/0.2 mm, 5.5 g (22.5 %) of the parent methane; at 230—240°/0.2—0.3 mm, 23.0 g (62 %) of the desired *p*-chlorobenzyl compound. After recrystallization from methanol the yield is 17.0 g (46 %) with m.p. 154—156°. (Found: C 81.51; H 5.45; N 3.82; Cl 9.46. (Calc. Cl 9.58).

p-*Chlorobenzyl-diphenyl-3-pyridylmethane.* A mixture of 24.5 g (0.1 mole) of diphenyl-3-pyridylmethane, 4.2 g of sodamide and 125 ml of dry toluene is refluxed for about 2 h. The evolution of ammonia is fairly strong at the beginning of the reflux and the contents soon become dark brown. The contents of the flask are cooled to about 80° and a solution of 17.0 (theoret. 16.1) g of *p*-chlorobenzyl chloride in 50 ml of dry toluene is added by means of a dropping funnel until the dark brown colour becomes pale and the contents appear clear (about half the amount of the solution is consumed for this purpose). The flask is now heated and the contents are refluxed for about half an hour. The contents are now cooled to about 80° again and the remaining chloride solution added by means of the dropping funnel. The flask is heated again and kept at reflux for one hour, after which time the evolution of ammonia has almost completely ceased. The reaction mixture is cooled to room temperature. The toluene layer is washed with water, dried and the toluene driven off. After a fore-run, giving 9.0 g of the parent methane, the *p*-chlorobenzyl derivative distils at 157—160°/0.1 mm. After recrystallization from a mixture of chloroform and methanol, 6.5 g (17.5 %) of white crystals with m.p. 174—175° are obtained. (Found: C 80.99; H 5.74; N 3.79).

3',3'-Dimethylbutyl-diphenyl-2-pyridylmethane was prepared from 0.05 mole of diphenyl-2-pyridylmethane as described for the *n*-octyl compound but with 9.0 (theoret. 8.25) g of *neo*hexyl (3,3-dimethylbutyl) bromide as alkylating agent. It was isolated after several recrystallizations from petroleum ether of the semisolid remainder from the toluene layer. Yield 6.5 g (39.5 %) of colourless crystals with m.p. 70.5—71.5°. (Found: C 87.73; H 8.31; N 4.28. Calc. for $C_{24}H_{27}N$ (329.5): C 87.49; H 8.26; N 4.25.)

3',3'-Dimethylbutyl-diphenyl-4-pyridylmethane was prepared analogously to the 2-isomer. It proved to be difficult to separate from the parent methane. After many recrystallizations from petroleum ether, a compound with m.p. 92—93.5° was obtained in low yield. (Found: C 87.78; H 8.36; N 4.26.)

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