[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF MARYLAND]

DERIVATIVES OF SPIRO[CYCLOHEXANE-1,1',3'-AMINOINDANS]

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An earlier communication (1) dealt with the preparation of spiro[cyclohexane-1,1',3'-aminoindans]. The biological investigation of these compounds indicated that a study of substances containing a substitutent in the aromatic ring of the parent compound was of import. This paper is a report on substitution reactions in the benzene nucleus of the spiro[cyclohexane-1,1',3'-aminoindans] and spiro[cyclohexane-1,1'-indanone-3']; the positon of the entering group was not absolutely confirmed.

PART A. NITRATION

Ingold and Piggott (2) have studied the nitration of indanone-1 and 1-aminoindan. The results of their work showed that the nitration of the ketone yielded predominately the 6-nitro compound and small amounts of the 4-nitro isomer, and correspondingly, the nitration of 1-aminoindan led almost entirely to the 1-amino-6-nitroindan and no 4-nitro isomer was obtained.

The reactions carried out in this work on the spiro[cyclohexane-1,1',3'-aminoindans] are shown in Figure 1 and the substitutions on spiro[cyclohexane-1,1'-indanone-3'] are given in Figure 2. Of particular interest in Figure 1 is the synthetic scheme originating with the nitration of spiro[cyclohexane-1,1',3'-dimethylaminoindan] which afforded an excellent yield of what seemed to be a single isomer, IIb. The nitro compound was catalytically reduced with Raney nickel to the corresponding diamine, IIIb, spiro[cyclohexane-1,1'-x'-amino-3'-dimethylaminoindan]. The diazonium compound prepared from the diamine could be converted to either the phenolic compound, spiro[cyclohexane-1,1',3'-dimethylamino-x'-hydroxyindan] (IV), by heating with aqueous sulfuric acid or to the nitrile (V) by treatment with cuprous cyanide. Acetylation of IIIb afforded VI which is of key importance in the subsequent section. Reduction of the amide VI with lithium aluminum hydride produced VII in good yields.

In order to determine whether different positional isomers would be obtained by starting with the ketone instead of the amine, spiro[cyclohexane-1,1'-indanone-3'] (VIII) was nitrated. In spite of all efforts to the contrary, we were able to isolate only what appeared to be a single isomer. This compound, spiro-[cyclohexane-1,1',x'-nitroindanone-3'] (IX), was fractionally crystallized many times; however, we were still unable to detect the presence of two species. The nitro compound was reduced in excellent yield with stannous chloride to the corresponding spiro[cyclohexane-1,1',x'-aminoindanone-3'] (X) and this substance was fractionally crystallized but only one compound could be isolated. Replacement of the amino group with a hydroxy group *via* diazotization afforded spiro[cyclohexane-1,1',x'-hydroxyindanone-3] (XI). This phenolic ketone was

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alkylated with ethyl sulfate and the product, XII, converted to the oxime. Reduction of the oxime in glacial acetic acid using Adams' catalyst led to spiro-[cyclohexane-1,1',3'-amino-x'-ethoxyindan] (XIII). The primary amine was converted to the N,N-dimethyl derivative (XIV) by the elegant procedure of Clarke, Gillespie, and Weisshaus (3) involving the use of formic acid and formaldehyde. The tertiary amine containing the ethoxy group in the aromatic nucleus was then treated with hydrobromic acid in glacial acetic acid to regenerate the phenolic compound, IV. Mixture melting point determination indicated that the resulting phenolic amine was the same isomer of spiro[cyclohexane-1,1',3'-dimethylamino-x'-hydroxyindan] as was obtained from the nitration and subsequent reactions shown in Figure 1 on spiro[cyclohexane-1,1',3'-dimethylaminoindan].

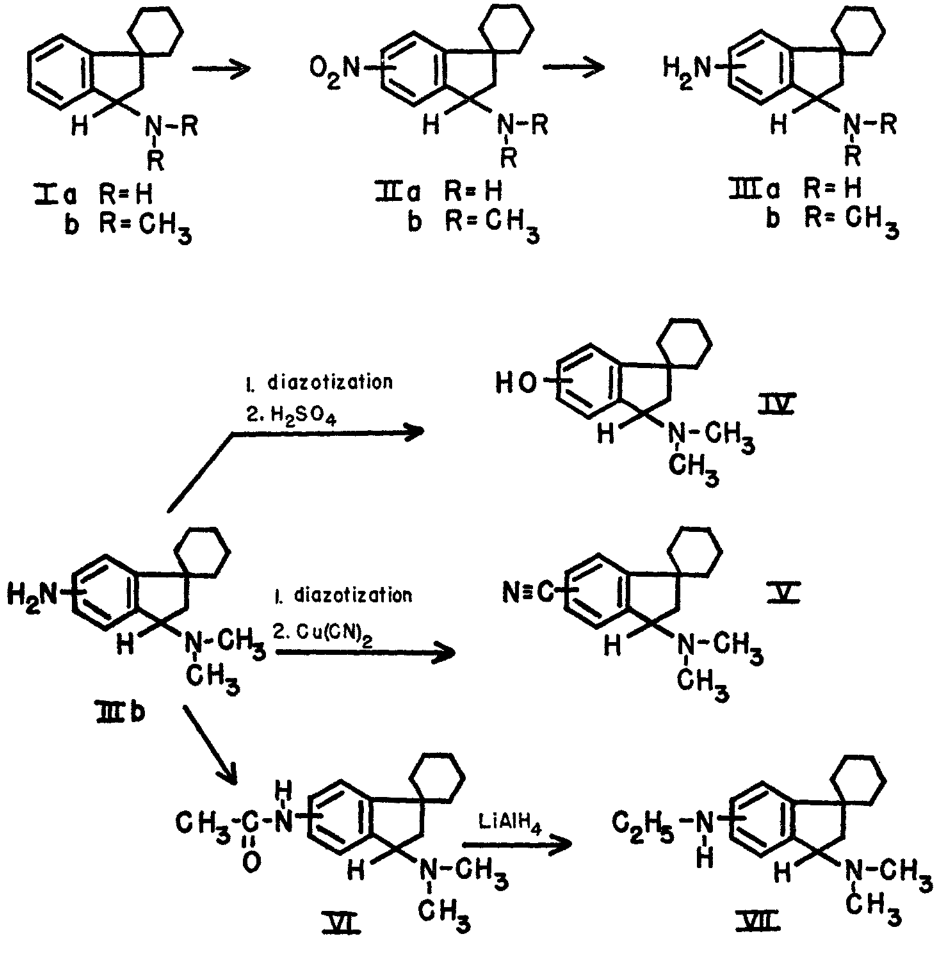

Fig. I

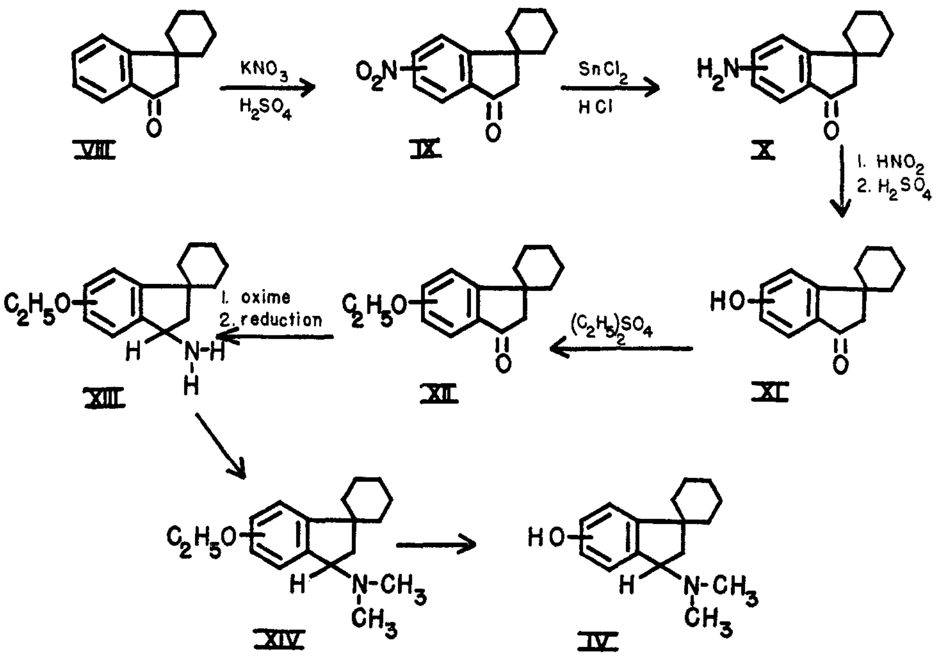

Fig. 2

EXPERIMENTAL[2]

Spiro[cyclohexane-1,1′,3′-dimethylamino-x′-nitroindan] (IIb). To a vigorously stirred solution of 2.3 g. (0.01 mole) of the amine (Ib) (1) in 4.3 ml. of concentrated sulfuric acid cooled to −10° was added dropwise a solution of 0.7 ml. of concentrated sulfuric acid and 0.7 ml. of fuming nitric acid (*sp. gr.* 1.5). After addition the mixture was stirred at 30° for an additional 1½ hours and then poured onto cracked ice. The yellow solid nitroamine bisulfate which separated was clarified in absolute alcohol and precipitated by the addition of dry ether; yield 2.2 g. or 59% of the white salt, m.p. 125–127°. The free nitroamine boils at 182–185°/1.8 mm.

Anal. Calc'd for $C_{16}H_{24}N_2O_6S$: C, 51.59; H, 6.50; N, 7.52.
Found: C, 50.77; H, 6.67; N, 7.14.

Spiro[cyclohexane-1,1′,3′-amino-x′-nitroindane) (IIa) was prepared in a similar manner as above in 59% yield by nitrating the primary amine, spiro[cyclohexane-1,1′,3′-aminoindan] (Ia). The nitroamine after recrystallization from methanol-water mixtures and sublimation at reduced pressure melted at 97–99°.

Anal. Calc'd for $C_{14}H_{18}N_2O_2$: C, 68.27; H, 7.37.
Found: C, 68.71; H, 7.57.

The amine hydrochloride formed in the usual manner and recrystallized from alcohol-ether mixtures melted at 268–273° (decomp.).

Anal. Calc'd for $C_{14}H_{19}ClN_2O_2$: C, 59.46; H, 6.77.
Found: C, 59.47; H, 6.97.

Spiro[cyclohexane-1,1′,x′-amino-3′-aminoindan] (IIIa) was prepared in 90% yield by the reduction of spiro[cyclohexane-1,1′,3′-amino-x′-nitroindan] in methanol at room temper-

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[2] The analyses reported in this paper were performed by Mrs. M. Aldridge and Mr. B. Baer of this laboratory.

ature and two atmospheres of hydrogen pressure with Adams' catalyst. This crystalline diamine, after recrystallization from ether-petroleum ether (20–40°) and sublimation at reduced pressure, melted at 129–131°.

Anal. Calc'd for $C_{14}H_{20}N_2$: C, 77.73; H, 9.32.
Found: C, 77.94; H, 9.27.

Spiro[cyclohexane-1,1',x'-amino-3'-dimethylaminoindan] (IIIb). The yellow liquid nitroamine (IIb) (5.2 g.) in 250 ml. of absolute ethanol was reduced at 29° and one atmosphere of hydrogen with about 0.5 g. of Raney nickel. The theoretical hydrogen absorption was achieved in 3¼ hours after which the absorption stopped. After removal of the catalyst and concentration of the solution under reduced pressure, 4.5 g. or 97% of a yellow solid was obtained. Clarification and recrystallization from petroleum-ether (90–100°) and finally sublimation at about 120° and 1 mm. produced the white crystalline product, IIIb, melting at 115–117°.

Anal. Calc'd for $C_{16}H_{24}N_2$: C, 78.63; H, 9.90.
Found: C, 78.72; H, 9.93.

The *N-acetyl compound* (VI) was prepared in the usual manner and after three recrystallizations from acetone melted at 183–184°.

Anal. Calc'd for $C_{18}H_{26}N_2O$: C, 75.48; H, 9.15.
Found: C, 75.67; H, 9.21.

Spiro[cyclohexane-1,1',3'-dimethylamino-x'-ethylaminoindane (VII). A solution of 1.5 g. of the N-acetyl derivative (VI) in 50 ml. of anhydrous benzene was added dropwise to 12 ml. of 1.3 *M* lithium aluminum hydride in ether. The mixture was stirred and refluxed for 18 hours and then decomposed in the cold with water. The organic layer was dried and concentrated to give 1.3 g. of red oil which formed a dihydrochloride when dry hydrogen chloride gas was passed into a dry ether solution of the diamine. This salt was recrystallized from alcohol-ether mixtures and melted at 183–188° (decomp.).

Anal. Calc'd for $C_{18}H_{30}Cl_2N_2$: C, 62.60; H, 8.76.
Found: C, 62.32; H, 8.90.

Spiro[cyclohexane-1,1',3'-dimethylamino-x'-hydroxyindan] (IV). A solution of the diamine (IIIb) in 2.2 ml. of concentrated sulfuric acid and 75 ml. of water was cooled to 0° and 1.1 g. of sodium nitrite in 10 ml. of water was added dropwise with stirring until a persistent test for nitrous acid was obtained. The excess nitrous acid was destroyed with urea, 10 ml. of 50% sulfuric acid was added, and the solution was heated on a steam-bath at 97° for one hour. The red solution was clarified and cooled to produce 1.75 g. of colorless crystals, which melted at 250–255° (decomp.) and whose analysis was consistent with the dihydrate of the phenol-amine sulfate.

Anal. Calc'd for $(C_{16}H_{23}NO)_2 \cdot H_2SO_4 \cdot 2H_2O$: C, 61.51; H, 8.39.
Found: C, 61.49; H, 8.50.

The *free amine* was regenerated with dilute ammonium hydroxide and after recrystallization from alcohol-water mixtures melted at 170–172°.

Anal. Calc'd for $C_{16}H_{23}NO$: C, 78.32; H, 9.45.
Found: C, 78.28; H, 9.58.

Spiro[cyclohexane-1,1',x'-cyano-3'-dimethylaminoindan] (V). A solution of 10 g. (0.041 mole) of the diazonium salt of spiro[cyclohexane-1,1',x'-amino-3'-dimethylaminoindan] (prepared as above) cooled to 0° was carefully neutralized with sodium bicarbonate. This solution was added dropwise to a freshly prepared mixture of 0.041 mole of cuprous cyanide covered with 200 ml. of toluene which was cooled to 0° and vigorously stirred. After the addition the mixture was stirred for a half hour at 0°, four hours at room temperature, and finally heated to 50° for three hours. The cooled mixture was made alkaline with sodium hydroxide and extracted with ether. The organic layer was extracted with dilute hydrochloric acid. The aqueous layer was neutralized, extracted with ether, dried, and the dried ether layer was concentrated under reduced pressure to yield 8 g. of a dark brown oil. The hydrochloride, made by passing hydrogen chloride gas into an ether solution of the amine, was dissolved in alcohol and treated with a few grams of stannous chloride and hydrochloric acid and finally charcoal to effect an efficient decolorization. The slightly yellowish hydrochloride was recrystallized from alcohol and melted at 257–260°.

Anal. Calc'd for $C_{17}H_{23}ClN_2$: C, 70.20; H, 7.97.

Found: C, 70.22; H, 8.05.

The *free cyanoamine*, spiro[cyclohexane-1,1′,x′-cyano-3′-dimethylaminoindan] (V), was regenerated with dilute ammonium hydroxide and after recrystallization from petroleum-ether (20–40°) and sublimation at reduced pressure it melted at 81–82°.

Anal. Calc'd for $C_{17}H_{22}N_2$: C, 80.26; H, 8.72.

Found: C, 80.20; H, 8.67.

Spiro[cyclohexane-1,1′,x′-nitroindanone-3′] (IX). Potassium nitrate (10 g.) in 30 ml. of concentrated sulfuric acid was added dropwise with stirring to a solution of 18.2 g. of spiro[cyclohexane-1,1′,-indanone-3′], (VIII) in 100 ml. of concentrated sulfuric acid cooled to 0° by means of an ice-salt bath. This addition took 1¼ hours and at no time was the temperature higher than 5°. The mixture was stirred an additional hour at 0° and poured with stirring onto cracked ice. The yellow solid was washed with water, dissolved in 500 ml. of hot acetone, clarified, and allowed to crystallize slowly overnight. In this manner, 13.7 g. of yellow hexagonal crystals melting at 193–194° was obtained; concentration of the mother liquors and finally addition of water produced further fractions which melted at 193–194° and gave no mixture melting point depression with the first fraction. Each fraction was then recrystallized from acetone, benzene, and then acetone, but in each case the melting point was 195–195.5° and gave no mixture melting point depression with other fractions. It seems probable therefore that nitration of the ketone under these conditions led to a single positional isomer. The total yield of nitroketone was 18 g. or 83%.

Anal. Calc'd for $C_{14}H_{15}NO_3$: C, 68.55; H, 6.17.

Found: C, 68.85; H, 6.22.

The orange *2,4-dinitrophenylhydrazone* made in the usual manner melted at 297–298° after recrystallization from alcohol.

Anal. Calc'd for $C_{20}H_{19}N_5O_6$: C, 56.47; H, 4.50.

Found: C, 56.51; H, 4.65.

Spiro[cyclohexane-1,1′,x′-aminoindanone-3′] (X). To a refluxing solution of 14.1 g. of the nitroketone (IX) in 90 ml. of 95% alcohol was added dropwise, with stirring, 41 g. of stannous chloride dihydrate in 40 ml. of concentrated hydrochloric acid and 20 ml. of 95% alcohol. After the addition, the yellow solution was refluxed an additional 30 minutes and then concentrated under reduced pressure. The residue was made strongly alkaline with potassium hydroxide so that all of the stannic hydroxide remained in solution and the solution extracted with ether. The ether extracts were washed until neutral and then dried over magnesium sulfate. After removal of the drying agent and concentration of the solution, a yellow solid was obtained which, after crystallization from benzene-petroleum ether (90–100°), yielded 11 g. or 82% of spiro[cyclohexane-1,1′,x′-aminoindanone-3′] melting at 116–118°. Further recrystallization from methanol-water mixtures and finally sublimation at 120° and 0.5 mm. produce a nearly white crystalline compound melting at 125–126°.

Anal. Calc'd for $C_{14}H_{17}NO$: C, 78.10; H, 7.96.

Found: C, 78.16; H, 8.24.

The aminoketone (10 g.) with 10 g. of hydroxylamine hydrochloride in 55 ml. of absolute alcohol and 23 ml. of pyridine was refluxed for three hours. The solution was concentrated to dryness under reduced pressure and the residue dissolved in alcohol, clarified, filtered, and the oxime precipitated by the slow addition of water. The *oxime* of spiro[cyclohexane-1,1′,x′-aminoindanone-3′] (10 g.) so obtained was recrystallized from methanol-water mixtures and melted at 178–180°.

Anal. Calc'd for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.88.

Found: C, 73.21; H, 8.00.

Spiro[cyclohexane-1,1′,-x′-hydroxyindanone-3′] (XI). A slurry of 10.5 g. of the aminoketone in 11 ml. of concentrated sulfuric acid and 80 ml. of water was stirred and cooled to

0° and 3.5 g. of sodium nitrite in 20 ml. of water was added dropwise over a period of 45 minutes. When a persistent test for nitrous acid was obtained, urea was added to destroy the excess nitrous acid. The solution was filtered and 5 ml. of concentrated sulfuric acid in 20 ml. of water was added to the filtrate and the solution heated on a steam-bath for 1¼ hours. The oily top layer which was formed from this reaction solidified on cooling. The crude, brown hydroxyketone was dissolved in ether, and the ether layer extracted with aqueous potassium hydroxide, clarified with charcoal, filtered, and neutralized in the cold with hydrochloric acid to produce 7.6 g. or 72% of yellow crystalline spiro[cyclohexane-1,1',x'-hydroxyindanone-3']. Further recrystallization from alcohol-water mixtures and finally sublimation at 160° and 0.03 mm. yielded a slightly yellow compound melting at 159–160°.

Anal. Calc'd for $C_{14}H_{16}O_2$: C, 77.74; H, 7.46.
Found: C, 77.41; H, 7.53.

The hydroxyketone (0.5 g.) was dissolved in 6 ml. of acetic anhydride and 2 ml. of pyridine was added. After standing for 48 hours at room temperature, the solution was concentrated under reduced pressure on a steam cone to yield a yellow oil which, when triturated with petroleum ether (20–40°), formed a crystalline mass. The *O-acetyl* compound, recrystallized from alcohol-water mixtures, melted at 100–101°.

Anal. Calc'd for $C_{16}H_{18}O_3$: C, 74.40; H, 7.02.
Found: C, 74.33; H, 7.25.

The *oxime* of spiro[cyclohexane-1,1',x'-hydroxyindanone-3'] prepared in the usual manner and recrystallized from alcohol-water mixtures melted at 182–184°.

Spiro[cyclohexane-1,1',x'-ethoxyindanone-3'] (XII). The hydroxyketone (XI) was ethylated with ethyl sulfate according to the directions for the preparation of veratraldehyde (4). The product was isolated by ether extraction of the alkaline medium. After drying and removal of the solvent, the residue was distilled at 155°/0.7 mm. The compound so obtained solidified and after recrystallization from petroleum ether (30–60°) and sublimation at 80° and 0.1 mm. it melted at 68–70°.

Anal. Calc'd for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25.
Found: C, 78.47; H, 8.54.

The yield of this reaction was low; however, the starting hydroxyketone could be recovered by acidification of the original reaction medium after the extraction with ether.

The *oxime* of spiro[cyclohexane-1,1',x'-ethoxyindanone-3'], prepared in the usual manner, was recrystallized from alcohol-water mixtures, and finally sublimed at reduced pressure; m.p. 151.5–152°.

Anal. Calc'd for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16.
Found: C, 74.34; H, 8.40.

Spiro[cyclohexane-1,1,3'-amino-x'-ethoxyindan] (XIII). The oxime of spiro(cyclohexane-1,1-x-ethoxyindanone-3) (2.7 g.) in 50 ml. of glacial acetic acid was hydrogenated at room temperature and 25 pounds of hydrogen using 0.1 g. of Adams' catalyst. After cessation of the absorption of hydrogen, the catalyst was filtered and the filtrate was cooled and made alkaline. The alkaline solution was extracted with ether, dried with magnesium sulfate, and concentrated to dryness after removal of the drying agent. The remaining brown oil was converted into the amine hydrochloride by passing hydrogen chloride gas through a dry ether solution of the amine. Recrystallization from methanol-ether mixtures produced 2.8 g. of the amine hydrochloride melting at 234–237°.

Anal. Calc'd for $C_{16}H_{24}ClNO$: C, 68.19; H, 8.58.
Found: C, 68.10; H, 8.79.

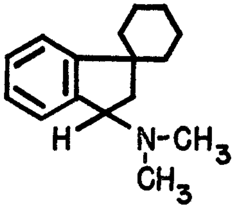
Spiro[cyclohexane-1,1',3'-dimethylamino-x'-ethoxyidan] (XIV). To a cooled solution of 5 ml. of 90% formic acid and 6 ml. of 40% formaldehyde was added 2.1 g. of the amine (XIII) hydrochloride and then the mixture was slowly warmed on a steam-bath until the evolution of carbon dioxide had ceased. The mixture was then concentrated under reduced pressure, made alkaline, and extracted with ether. The ether layer was extracted with dilute hydrochloric acid, which in turn was neutralized, extracted with ether and the ether extract dried over magnesium sulfate. After removal of the drying agent, dry hydrogen chloride gas was passed into the solution to give 2 g. of crystalline amine hydrochloride, which after recrystallization from acetone melted at 211–213°.

Anal. Calc'd for $C_{18}H_{28}ClNO$: C, 69.77; H, 9.11.

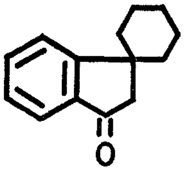
Found: C, 69.88; H, 9.37.

The amine hydrochloride (1.8 g.) dissolved in 11 ml. of glacial acetic acid and 10 ml. of 48% hydrobromic acid was refluxed for 4½ hours and then poured onto ice. The brown solid precipitate so formed was clarified and crystallized from alcohol-water mixtures to give 1.3 g. of white crystalline material melting at 170–172° and giving no mixture melting point depression with spiro[cyclohexane-1,1′,3′-dimethylamino-x′-hydroxyindane] (IV).

PART B. FRIEDEL-CRAFTS REACTION



Ib



VIII

Nitration of Ib and VIII occurred in the aromatic nucleus and the position of the nitro group was shown in Part A by chemical transformations to be the same, almost certainly in the 5′ or 7′ position. The numbering system (Ring Index) (5) is illustrated in Figure 3. This section contains the results of another electrophilic reaction, the Friedel-Crafts reaction, on Ib, and the conversion of these products to other substances; also an attempt which was unsuccessful to obtain exact proof of the location of substituted groups.

Fig. 3

In general, the Friedel-Crafts reaction in the preparation of amino ketones has not been very successful since attempts to use aluminum chloride for the introduction of an acyl group into the aromatic ring of N-dialkylamine have led to complex condensation products. However, the *p*-acylarylamides are obtained in good yields from the reaction of N-arylacetamides with acylhalides in the presence of aluminum chloride (6). As expected from the above, it was found that spiro[cyclohexane-1,1′,3′-dimethylaminoindan] (Ib) gave very complex condensation products in the Friedel-Crafts reaction with acetyl chloride and aluminum chloride. Surprising, however, was the fact that the corresponding ketoamines, XV, were obtained in reasonable yield in the reaction of the amine, Ib, with acetic anhydride, propionic anhydride, and *n*-butyryl chloride. Reduction of these ketoamines with lithium aluminum hydride produced the aminoalcohols, XVI, as shown in Fig. 4.

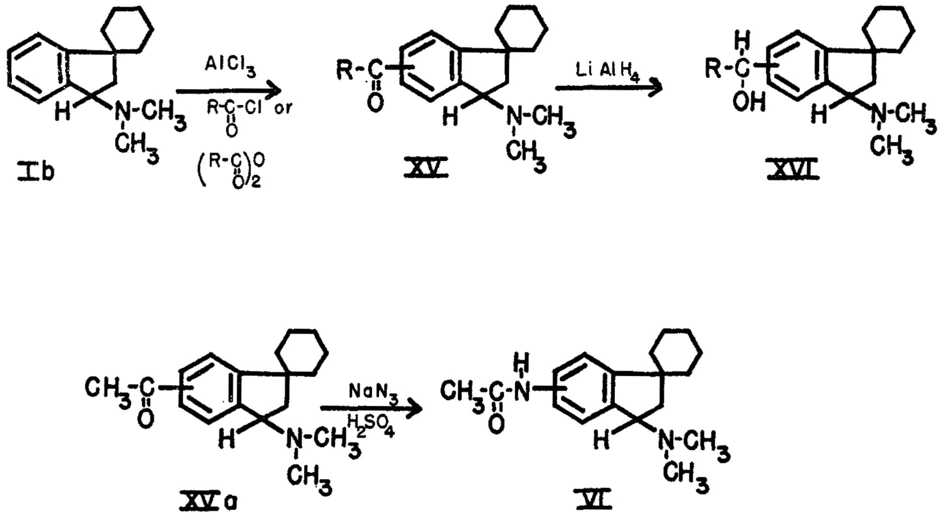


Fig. 4

It is particularly fortunate that the Schmidt reaction on spiro[cyclohexane-1,1′,x′-acetyl-3′-dimethylaminoindan] (XVa) gave an excellent yield of the amide VI, since it was found that this compound was identical with the substance prepared by the nitration of spiro[cyclohexane-1,1′,3′-dimethylaminoindan] (Ib), and subsequently converted to the amide by reduction of the nitro group followed by acetylation of the amine. This result establishes first that the nitration of Ib and VIII and the Friedel-Crafts reaction on Ib yielded single isomers, and secondly that the position of the entering group was the same in all three instances.

Notwithstanding the above conclusions, one still cannot elect between positions 5′ and 7′ for the location of the various substituents, although, an examination of the mass of chemical literature would indicate that the 5′ position is the most likely. Quarternary salts or acid solutions of aromatic amines lead exclusively to *meta* orientation. The introduction of methylene groups between a positive pole and an aromatic nucleus diminishes the *meta*-orienting effect; ionized benzylammonium salts are nitrated largely (88%), but not wholly, in the *meta* position (7). Closely related to the work reported in this paper is the study of Ingold and Piggott (2) on the nitration of 1-aminoindan which led exclusively to 1-amino-6-nitroindan.

Oxidation of spiro[cyclohexane-1,1′,x′-nitroindanone-3′] (IX) was attempted in order to define the position of the substituent, but the oxidation was unsuccessful in our hands. If a nitrophthalic acid had been obtained as the product of oxidation, a differentiation between positions 5′ and 6′ or 4′ and 7′ still could not have been made.

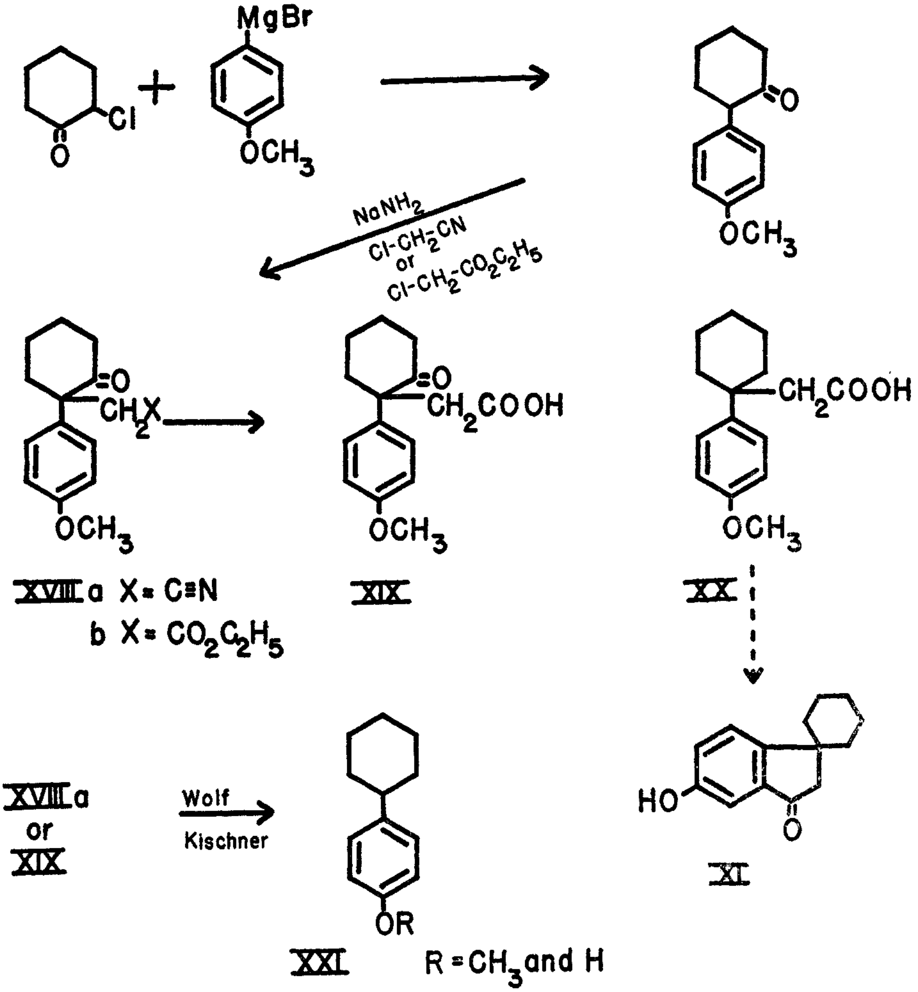


Fig. 5

The product of nitration of spiro[cyclohexane-1,1′-indanone-3′] was converted by a series of steps (see Fig. 2) to a phenolic ketone, XI. Since the evidence cited above would indicate the most likely structure of this ketone to be spiro-[cyclohexane-1,1′,5′-hydroxyindanone-3′], it was decided to attempt to prepare by unequivocal methods substance XI as shown in Fig. 5.

Hydrolysis of the nitrile XVIIIa led to a complex mixture, the separation of which was unsuccessful, but the ester XVIIIb was hydrolyzed to the acid XIX.

Bockelheide and Schilling (8) have reported the preparation of XVIII a and b but without the methoxyl group, and in a private communication, Dr. Boekelheide stated that ketone derivatives were difficult to obtain and hydrolysis of the nitrile led largely to lactone formation. To avoid the difficulty caused by the keto group, the Wolf-Kischner reaction was explored on both the nitrile XVIIIa and the acid XIX in an unsuccessful attempt to prepare XX, cyclization of which would have yielded the desired substance, XI. Unexpectedly, *p*-cyclohexylanisole and XXI, *p*-cyclohexylphenol, were obtained from the nitrile XVIIIa while only *p*-cyclohexylphenol was obtained from the acid XIX. Side chain eliminations of this type are not entirely without precedence (9), however, the results obtained from the Wolf-Kischner reaction on XVIIIa and XIX excluded the possibility of preparing XI from 1-anisyl-1-carboxymethylcyclohexane by ring closure and demethylation of the ether.

The authors wish to acknowledge that this investigation was supported in part by a research grant from the Eli Lilly Company.

EXPERIMENTAL

Spiro[cyclohexane-1,1',x'-acetyl-3'-dimethylaminoindane (XVa). A solution of 8 g. of acetic anhydride in 30 ml. of carbon disulfide was added with vigorous stirring to a mixture of 14 g. of spiro[cyclohexane-1,1',3'-dimethylaminoindan], 30 g. of anhydrous aluminum chloride, and 130 ml. of carbon disulfide. A vigorous reaction ensued, which caused hydrogen chloride to be evolved, and which caused the carbon disulfide to reflux. After the initial reaction had subsided, the mixture was refluxed for an additional 18 hours. The cooled mixture was then poured with stirring into an ice-sodium hydroxide solution and the organic layer extracted with ether. The ether layer was extracted with dilute hydrochloric acid, the aqueous layer made alkaline, extracted with ether, and dried over magnesium sulfate. After removal of the drying agent by filtration, distillation yielded 5 g. of unreacted amine (b.p. 96–106°/0.08–0.09) and 5.7 g. of spiro[cyclohexane-1,1',x'-acetyl-3'-dimethylaminoindan] which boiled at 145–160° at 1 mm. The ketoamine was crystallized from petroleum ether (20–40°) in a Dry Ice-bath and after two sublimations melted at 90–92°.

Anal. Calc'd for $C_{18}H_{25}NO$: C, 79.66; H, 9.29.
Found: C, 79.62; H, 9.52.

The *hydrochloride* made in the usual manner was recrystallized from methanol-ether mixtures and melted at 254–255° (decomp.).

Anal. Calc'd for $C_{18}H_{26}ClNO$: C, 70.22; H, 8.51.
Found: C, 70.15; H, 8.93.

Spiro[cyclohexane-1,1',x'-propionyl-3'-dimethylaminoindan] (XV). In the same manner as above, 7 g. of the amine (Ib), 14 g. of anhydrous aluminum chloride, and 4.3 g. of propionic anhydride was allowed to react in carbon disulfide to produce 4.3 g. of recovered amine (Ib) and 1.5 g. of spiro[cyclohexane-1,1',x'-propionyl-3'-dimethylaminoindan] b.p. 155°/0.5 mm., m.p. 56–58° from petroleum ether (20–40°).

Anal. Calc'd for $C_{19}H_{27}NO$: C, 79.95; H, 9.54.
Found: C, 80.06; H, 9.66.

The *hydrochloride* made in the usual manner was recrystallized from alcohol-ether mixtures and melted at 252–255°.

Anal. Calc'd for $C_{19}H_{28}ClNO$: C, 70.89; H, 8.77.
Found: C, 71.03; H, 8.98.

Spiro[cyclohexane-1,1',x'-(n-butyryl)-3'-dimethylaminoindan] (XV). In the same manner as above, 7 g. of the amine (Ib), 11 g. of anhydrous aluminum chloride, and 3.5 g. of *n*-butyryl chloride was allowed to react in carbon disulfide to produce 1.5 g. of unreacted amine (Ib) and 4.4 g. of spiro[cyclohexane-1,1′,x′-(*n*-butyryl)-3′-dimethylaminoindan]; b.p. 150°/0.4 mm., m.p. 48–49° from petroleum-ether (20–40°).

Anal. Calc'd for $C_{20}H_{29}NO$: C, 80.22; H, 9.76.

Found: C, 80.57; H, 9.99.

The *hydrochloride* made in the usual manner was recrystallized from alcohol-ether mixtures and melted at 215–218°.

Anal. Calc'd for $C_{20}H_{30}ClNO$: C, 71.54; H, 9.00.

Found: C, 71.71; H, 8.82.

Spiro[cyclohexane-1,1′,x′-acetylamino-3′-dimethylaminoindan] (VI). A mixture of 1 g. of spiro[cyclohexane-1,1′,x′-acetyl-3′-dimethylaminoindan] in 20 ml. of benzene and 2.2 ml. of 90% sulfuric acid was stirred and heated to 40–45° and 0.36 g. of powdered sodium azide was added portionwise. The mixture evolved gas for about five minutes after the addition of the sodium azide. The mixture was stirred for an additional 20 minutes and the organic layer was extracted with water. The aqueous amine sulfate layer was made alkaline, extracted with ether, dried, and concentrated to give 0.7 g. of a white crystalline compound, spiro[cyclohexane-1,1′,x′-acetylamino-3′-dimethylaminoindan]. After recrystallization from benzene and acetone, the substance melted at 182–183°, and gave no mixture melting point depression with the compound prepared by the acetylation of spiro[cyclohexane-1,1′,x′-amino-3′-dimethylaminoindane].

Anal. Calc'd for $C_{18}H_{26}NO$: C, 75.48; H, 9.15.

Found: C, 75.67; H, 9.21.

Spiro[cyclohexane-1,1′,3′-dimethylamino-x′-(1-hydroxyethyl)indan] (XVI). To an efficiently stirred solution of 20 ml. of 1.3 *M* lithium aluminum hydride in ether was added dropwise 3 g. of spiro[cyclohexane-1,1′,x′-acetyl-3′-dimethylaminoindan] in 100 ml. of anhydrous ether. After the addition, the mixture was stirred for an additional half-hour and then sufficient water was added in the cold to just decompose the excess reagent and the complex. The ether layer was washed with water, dried over magnesium sulfate, and after removal of the drying agent, concentrated to give 3 g. of the hydroxy compound. Since the substance was difficult to handle, the hydrochloride was prepared by passing dry hydrogen chloride gas through an ether solution of the amine and after recrystallization from alcohol-ether mixtures melted at 245–247°.

Anal. Calc'd for $C_{18}H_{28}ClNO$: C, 69.77; H, 9.11.

Found: C, 69.45; H, 9.21.

Spiro[cyclohexane-1,1′,3′-dimethylamino-x′-(1-hydroxybutyl)indan] (XVI). In the same manner as above, 3.4 g. of spiro[cyclohexane-1,1′,x′-(*n*-butyryl)-3′-dimethylaminoindan] was reduced with lithium aluminum hydride to yield 3.4 g. of the hydroxy compound which was then converted to the hydrochloride; m.p. 210–211°, after recrystallization from alcohol-ether mixtures.

Anal. Calc'd for $C_{20}H_{32}ClNO$: C, 71.08; H, 9.55.

Found: C, 70.98; H, 9.69.

2-(p-Anisyl)-2-cyanomethylcyclohexanone (XVIIIa). 2-*p*-Anisylcyclohexanone (46 g.) (10), prepared in 69% yield from 2-chlorocyclohexanone (11), and *p*-anisylmagnesium bromide in 100 ml. of ether and 200 ml. of benzene were added dropwise to a vigorously stirring mixture of 20 g. of sodamide in 175 ml. of ether and 125 ml. of benzene. This mixture was stirred and refluxed for an additional 3½ hours (no further evolution of ammonia). The mixture was cooled and 39 g. of chloroacetonitrile in 150 ml. of ether was added dropwise. The reaction mixture was stirred and refluxed for 24 hours, and then decomposed with water. The organic layer was separated, washed, dried and distilled. 2-(*p*-Anisyl)-2-cyanomethylcyclohexane was distilled with a Hickman still at a bath temperature of 190–200° at 0.07 mm.; yield 40 g. (73%) of solid which melted at 74–77° after recrystallization from petroleum ether (60–80°) and sublimation at reduced pressure.

Anal. Calc'd for $C_{15}H_{17}NO_2$: C, 74.04; H, 7.04.

Found: C, 73.93; H, 7.09.

2-p-Anisyl-2-carboxymethylcyclohexanone (XIX). In a manner similar to the preparation of XVIIIa, 16 g. of 2-*p*-anisylcyclohexanone in 50 ml. of benzene was added dropwise with stirring to a mixture of 3.5 g. of sodamide in 75 ml. of ether. The mixture was refluxed and stirred for 2½ hours (no further evolution of ammonia), and then 15 g. of ethyl bromoacetate in 30 ml. of ether was added dropwise. This mixture was refluxed and stirred for 2½ hours and allowed to stand at room temperature for 16 hours. The organic layer was washed with water, dried, and distilled to yield 17.5 g. of 2-(*p*-anisyl)-2-carbethoxymethylcyclohexanone, b.p. 160–165°/0.3 mm.; which was hydrolyzed directly with aqueous potassium hydroxide. After the cooled hydrolysis mixture was extracted with ether, the aqueous layer was slowly acidified to produce 2-(*p*-anisyl)-2-carboxymethylcyclohexanone (XIX) which melted at 149–150° after recrystallization from benzene-petroleum ether (30–60°) mixtures.

Anal. Calc'd for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92.
Found: C, 69.21; H, 6.99.

Wolf-Kischner on 2-(p-anisyl)-2-cyanomethylcyclohexanone. A mixture of 5 g. of 2-(*p*-anisyl)-2-cyanomethylcyclohexanone, 4.1 g. of potassium hydroxide, 10.5 ml. of 85% hydrazine hydrate, and 27 ml. of diethylene glycol was refluxed for one hour (12). The mixture was then distilled in order to raise the temperature to 195–200°; during this process, a substance, semisolid in nature, distilled over together with water and diethylene glycol. This solid, after recrystallization from alcohol-water mixtures and sublimation at reduced pressure, melted at 54–56° and gave no mixture melting point depression with an authentic sample of *p*-cyclohexylanisole prepared by the Wolf-Kischner reduction on 2-*p*-anisylcyclohexanone.

Anal. Calc'd for $C_{13}H_{18}O$: C, 82.06; H, 9.54.
Found: C, 82.01; H, 9.60.

After the temperature of the Wolf-Kischner reaction medium had attained 195–200°, heating under reflux conditions was continued for four hours. Steam-distillation of the acidified reaction medium yielded crude *p*-cyclohexylphenol which, after recrystallization from alcohol-water mixtures and sublimation at reduced pressure, melted at 125–127°. This material gave no mixture melting point depression with an authentic sample of *p*-cyclohexylphenol prepared by demethylation of *p*-cyclohexylanisole.

Anal. Calc'd for $C_{12}H_{16}O$: C, 81.77; H, 9.15.
Found: C, 81.90; H, 9.11.

Wolf-Kischner on 2-(p-anisyl)-2-carboxymethylcyclohexanone (XIX). In a manner similar to that above, 0.6 g. of acid XIX, 0.5 g. of potassium hydroxide, 1.3 ml. of 85% hydrazine hydrate, and 10 ml. of diethylene glycol were refluxed for 1½ hours, after which the temperature of the solution was raised to 195–200° by distillation. The solution was refluxed at this temperature for 4½ hours, poured onto ice, and acidified to yield 0.4 g. of crude *p*-cyclohexylphenol. After recrystallization from alcohol-water mixtures and sublimation at reduced pressure the white crystalline material melted at 126–127° and gave no mixture melting point depression with an authentic sample of *p*-cyclohexylphenol.

Anal. Calc'd for $C_{12}H_{16}O$: C, 81.77; H, 9.15.
Found: C, 82.04; H, 9.26.

SUMMARY

The nitration of spiro[cyclohexane-1,1',3'-aminoindans] and spiro[cyclohexane-1,1'-indanone-3'] has been studied. It is shown that the position of the entering group is the same in the nitration of the amino compound and the keto compound. The nitro group was converted by standard methods to the amino group, and replaced by phenolic hydroxide, nitrile, etc. The Friedel-Crafts reaction has been used on spiro[cyclohexane-1,1',3'-dimethylaminoindan] to prepare a series of acyl compounds. These ketoamines were reduced to the corresponding aminocarbinols. The Schmidt reaction on spiro[cyclohexane-1,1',x'-

acetyl-3′-dimethylaminoindan] readily afforded an amide and this amide was shown to be the same as the compound formed by the acetylation of spiro[cyclohexane-1,1′,x′-amino-3′-dimethylaminoindan]. This proves that the two electrophilic reactions, Friedel-Crafts and nitration, yield exclusively the same positional isomer with spiro[cyclohexane-1,1′,3′-dimethylaminoindan] and moreover that this position is the same as that obtained by nitration of spiro-[cyclohexane-1,1′-indanone-3′]. Evidence is cited which would indicate that the position is the 5′-position, but an attempt to prove this by an unequivocal synthesis failed.

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