SYNTHESIS OF SOME 3,3-DIMETHYL-1-AMINOINDANS

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We recently reported on the synthesis of a series of substituted spiro (cyclohexane-1,1,3-aminoindans), the structure of which is given below, Fig. IA. The results of biological tests on these compounds were such that an examination of other closely related substances were indicated. Accordingly, a number of substituted 3,3-dimethyl-1-aminoindans have been prepared. (Fig. IB) The line of reasoning was that replacement of the spirocyclohexyl group by two methyl groups did not constitute a major alteration in the molecule. The substances which were prepared and tested showed no analgetic activity.



One group of compounds was prepared by standard procedures as shown in Fig. II. The starting material, 3,3-dimethyl-1-indanamine was obtained from 3,3-dimethyl-1-indanone.



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This latter substance had been prepared by Koelsch and LeClaire (2) by condensation of mesityl oxide and benzene in the presence of aluminum chloride followed by the hypochlorite oxidation of the resulting methyl ketone. Cyclization of the acid with sulfuric acid or of the acid chloride with aluminum chloride in the usual manner was readily effected. Our attempts to oxidize V (careful examination indicated only one isomer) were fruitless since the conditions which were sufficiently drastic to remove the side chain caused oxidation of the total molecule.

The second group of substances was prepared by the substitution in the aromatic nucleus of 3,3-dimethyl-1-indanone with the subsequent conversion of the keto group to an amino group as shown in Fig. III. The position of the nitro group in IX and V was assigned on the basis of the work done by Ingold and Pigott (3) and by Koelsch and LeClaire, cited above; the latter workers had prepared IX and assigned it this structure. In addition, the earlier work (1) on substitution reactions on both the keto and amino compounds of the closely related spirocyclohexylindans (Fig. IA) had proved that the entering group in each case was in the same position, almost certainly the 6-position.



A more convincing proof that the substituents in the above indans are in the six position rests upon the sequence of reactions shown in Fig. IV.

One interesting observation was made in this series. The ketone XII (Fig. III) melted at 32°; the sample of the ketone prepared as shown in Figure IV was slightly impure and could not be obtained sufficiently pure for comparison. Instead the oxime (XIII) and the 2,4-dinitrophenylhydrazone of XII were used for identification. However, the original oxime (XIII) (Fig. III) melted at 137–138°, the latter, Fig. IV, at 105–106°; but the lower-melting product was

shown to be one of the geometrical forms, for when some of this oxime was heated for a short time at 150° and then recrystallized, the form melting at 136-138° was isolated. The same conversion was accomplished by dissolving the low-melting form of the oxime in higher boiling petroleum ether, and evaporating the solution to dryness on the steam-bath. Both derivatives were identical with those prepared as shown in Fig. III.



EXPERIMENTAL³

1-Amino-3,8-dimethylindan (III). A solution of 3,3-dimethyl-1-indanone (II) (53 g., 0.33 mole), 77 g. (1.1 moles) of hydroxylamine hydrochloride, 140 ml. of pyridine, and 350 ml. of absolute ethanol was heated under reflux for ten hours. The excess pyridine and alcohol was removed by distillation under reduced pressure. The residue was added to water and the oxime was extracted with ether. After drying of the ethereal solution the oxime was isolated by distillation under reduced pressure. An infrared lamp was very useful to keep the distillate more fluid. The oxime of 3,3-dimethyl-1-indanone (53 g.; 91%) boiled at 123-125°/1 mm. and was very viscous. All attempts to crystallize the substance failed as did attempts to isolate two forms.

Anal. Calc'd for C₁₁H₁₃NO: C, 75.40; H, 7.48.

Found: C, 75.49; H, 7.60.

The hydrochloride of the oxime was prepared by passing hydrogen chloride into an anhydrous ethereal solution of the oxime; m.p. 135-137° after recrystallization from ether-absolute ethanol.

Anal. Calc'd for C₁₁H₁₄ClNO: C, 62.40; H, 6.66.

Found: C, 62.22; H, 6.92.

Catalytic reduction of the oxime (64 g., 0.36 mole) in ethanol saturated with ammonia was accomplished at 75-80° with Raney nickel and a pressure of 3000 p.s.i. After filtration the residue was distilled; 3,3-dimethyl-1-aminoindan (55 g., 92%) was obtained. A purified sample (regenerated from the hydrochloride of the amine) had a n_{p}^{24} 1.5180 and boiled at 65°/1.5 mm.

Anal. Calc'd for C₁₁H₁₆N: C, 81.96; H, 9.38. Found: C, 82.11; H, 9.55.

³ We wish to express our appreciation to Mrs. Mary Aldridge of this laboratory for the analyses reported in this paper.

The hydrochloride was prepared by the method described above, and after recrystallization from anhydrous ether-absolute ethanol melted at 225-227°.

Anal. Cale'd for C₁₁H₁₆ClN: C, 66.82; H, 8.16.

Found: C, 66.79; H, 8.28.

The N-acetyl derivative of the amine prepared in the usual manner melted at 144–145° after recrystallization from ethanol-water.

Anal. Cale'd for C₁₃H₁₇NO; C, 76.80; H, 8.43.

Found: C, 76.89; H, 8.52.

3,3-Dimethyl-1-dimethylaminoindan (IV). Compound III as the hydrochloride (45.5 g.) was converted to the dimethylamino compound (IV) by the excellent procedure of Clarke, Gillespie, and Weisshaus (4) using formic acid and formaldehyde. The product was isolated in the usual manner; yield 35.5 g. of the free tertiary amine which distilled at 77-80°/1-2 mm., n_p^{24} 1.5164.

Anal. Cale'd for C13H19N: C, 82.48; H, 10.12.

Found: C, 82.50; H, 10.35.

The hydrochloride of IV was prepared by passing hydrogen chloride into an anhydrous ethereal solution of the tertiary amine. The white crystalline compound was recrystallized from absolute ethanol-ether, m.p. 200-201°.

Anal. Calc'd for C₁₃H₂₀ClN: C, 69.16, H, 8.93.

Found: C, 69.16; H, 9.02.

6-Nitro-3,3-dimethyl-1-dimethylaminoindan (V). 3,3-Dimethyl-1-dimethylaminoindan (19 g., 0.1 mole) was added to 250 ml. of conc'd sulfuric acid. While this solution was chilled at 5° or lower 11.2 g. of finely powdered potassium nitrate was added slowly. The solution was finally warmed to 30-40° for one hour and then poured into ice. This medium was made alkaline with concentrated ammonium hydroxide and extracted with ether. The ether extract was decolorized with carbon black and dried. Hydrogen chloride was passed into the solution and the recrystallization of the product from absolute ethanol yielded a creamy-white sample of 6-nitro-3,3-dimethyl-1-dimethylaminoindan hydrochloride (19 g.) melting at 253-255°.

Anal. Calc'd for C₁₃H₁₉ClN₂O₂: C, 57.67; H, 7.07.

Found: C, 57.71; H, 7.19.

A sample of the hydrochloride was added to water, conc'd ammonium hydroxide was added, and the mixture was extracted with ether. The ether layer was dried and the ether was removed under reduced pressure. The solid residue was sublimed under reduced pressure and the sublimate was crystallized from petroleum ether (20-40°). Pale yellow 6-nitro-3,3dimethyl-1-dimethylaminoindan, m.p. 57-58°, was obtained. The free amine darkens considerably upon standing and several times an explosion occurred upon combustion for analysis.

Anal. Calc'd for C₁₃H₁₈N₂O₂: C, 66.64; H, 7.74.

Found: C, 66.74; H, 7.80.

6-Amino-3,3-dimethyl-1-dimethylaminoindan (VI). The catalytic reduction of the nitro compound (V) as the hydrochloride was accomplished in the standard manner; 36 g. of V in 150 ml. of 95% ethanol was reduced with 5% palladinized charcoal at 1500 p.s.i. The catalyst was removed by filtration, the filtrate was made alkaline with ammonium hydroxide, and the diamine was extracted with ether. The ether extract was dried with magnesium sulfate. After removal of the ether under reduced pressure an orange-white mass of solid material was obtained which was recrystallized from petroleum ether ($30-60^\circ$). 6-Amino-3,3-dimethyl-1-dimethylaminoindan (which melted at 109°) was obtained in a white crystalline state (26 g.). Unlike the nitroamine, its precursor, the free diamine VI, was stable to air oxidation.

Anal. Calc'd for C13H20N2: C, 76.42; H, 9.87.

Found: C, 76.56; H, 9.98.

The *dihydrochloride* could not be obtained as a solid by passing hydrogen chloride gas into a dry ethereal solution of the diamine. The solid which did form was extremely hygroscopic and only oily material resulted. The *N*-acetyl derivative of VI was obtained in the usual manner using acetic anhydridesodium acetate. This derivative was recrystallized from petroleum ether (60–80°) and melted at 146–147°.

Anal. Calc'd for C₁₅H₂₂N₂O: C, 73.14; H, 9.01.

Found: C, 73.35; H, 9.16.

6-Hydroxy-3,3-dimethyl-1-dimethylaminoindan (VII). The diamine (V) (25 g., 0.12 mole) was dissolved in a solution of 18.2 ml. of conc'd sulfuric acid in 300 ml. of water. To this solution at 0°, 9.6 g. of sodium nitrite in 60 ml. of water was added dropwise and with stirring.

Excess nitrous acid was destroyed by the addition of a small amount of urea. Into this solution was poured a mixture of 45 ml. of conc'd sulfuric acid in 30 ml. of water, and the whole was heated on the steam-bath. Around 75-80° a vigorous evolution of nitrogen began; heating was continued for a further two hours. The solution was cooled, adjusted to pH 6 with ammonium hydroxide, and extracted four times with ether. The hydroxyamine was removed from the ether layer by extraction with HCl, the aqueous solution again was adjusted to pH 6, and the whole was extracted with ether. A considerable amount of a colored impurity was removed by this step. The resulting ethereal solution was decolorized with charcoal, dried with magnesium sulfate, and the ether was removed under reduced pressure. The crude, solid aminophenol (21 g.) which was obtained was first dissolved in ether which solvent was then displaced by petroleum ether. The white crystalline 6-hydroxy-3,3-dimethyl-1-dimethyl-aminoindan melted at 159-160°.

Anal. Calc'd for C₁₃H₁₉NO: C, 76.05; H, 9.33.

Found: C, 76.58; H, 9.50.

The hydrochloride was obtained by passing dry hydrogen chloride into a dry ethereal solution of the hydroxyamine. Recrystallization of the hydrochloride from absolute ethanolether yielded material melting at 197-201° which was somewhat hygroscopic. The analysis indicated a one-half molecule of ethanol of crystallization.

Anal. Calc'd for C13H20ClNO. 1/2C2H5OH: C, 63.50; H, 8.75.

Found: C, 63.60; H, 8.47.

Sublimation of the above solvated compound at reduced pressure yielded the pure *hydrochloride*, m.p. 108-110°, which was extremely hygroscopic.

Anal. Calc'd for C₁₃H₂₀ClNO: C, 64.58; H, 8.34.

Found: C, 64.38; H, 8.26.

6-Acetyl-3, 3-dimethyl-1-dimethylaminoindan (VIII). Compound VII (13 g.), the free hydroxyamine, was allowed to react with acetic anhydride (80 ml.) and sodium acetate (35 g.) in the usual manner. The reaction mixture was poured into ice and the solution was make alkaline with cone'd ammonia and extracted with ether. After drying of the extract and removal of the ether under reduced pressure the residue was distilled to yield the somewhat colored 6-acetoxy compound. Redistillation gave a colorless sample (8.0 g.); b.p. 128-131°/2.5 mm. This compound was not too stable.

It was converted to the hydrochloride of 6-acetoxy-3,3-dimethyl-1-dimethylaminoindan in the manner described above. This material melted at 228°.

Anal. Calc'd for C₁₅H₂₂ClNO₂: C, 63.48; H, 7.82.

Found: C, 63.59; H, 8.00.

6-Nitro-3,3-dimethyl-1-indanone (IX). 3,3-Dimethyl-1-indanone (32 g.) was nitrated as described for compound IV to yield 38 g. of product. The ethereal extract after evaporation provided the crude solid which after recrystallization from methanol melted at 133-134° [Lit: (2) 133-134°].

Anal. Calc'd for C₁₁H₁₁NO: C, 64.38; H, 5.40.

Found: C, 64.51; H, 5.62.

The orange 2,4-dinitrophenylhydrazone, prepared in the usual manner, melted at 315-318° after recrystallization from ethyl acetate-toluene.

Anal. Calc'd for C17H15N5O6: C, 52.99; H, 3.93.

Found: C, 53.29; H, 4.02.

6-Amino-3, 3-dimethyl-1-indanone (X). The nitroketone (IX) (43 g.) in 150 ml. of absolute

ethanol was catalytically reduced with 5% palladinized carbon at room temperature and a pressure of 1800 p.s.i. After filtration and removal of the alcohol under reduced pressure a dark red liquid was obtained. This was dissolved in ether and the ether was extracted with 5% hydrochloric acid. The aqueous extract was made alkaline with conc'd ammonia and this solution was extracted with ether. After drying and removal of the last traces of ether under reduced pressure a red crystalline material was obtained which, after several decolorizations and recrystallizations from petroleum ether (80–120°), gave peach-colored crystals (28 g., m.p. 83–84°) of 6-amino-3,3-dimethyl-1-indanone.

Anal. Calc'd for C₁₁H₁₃NO: C, 75.40; H, 7.48.

Found: C, 75.24; H, 7.38.

The hydrochloride of X was too unstable to be obtained in satisfactory form, but the white crystalline N-acetyl derivative was prepared in the usual manner and, after recrystallization from absolute ethanol-petroleum ether $(60-80^{\circ})$ melted at $123-124^{\circ}$.

6-Hydroxy-3,3-dimethyl-1-indanone (XI). The diazotization of compound X and the decomposition of the diazonium intermediate to yield compound XI was performed essentially as described for the preparation of compound VII. The hydroxyketone (17 g. from 25 g. of amino ketone) was recrystallized from ethanol-water. A sample purified further by sublimation and recrystallization melted at 113-114°.

Anal. Calc'd for C₁₁H₁₂O₂: C, 74.97; H, 6.87.

Found: C, 75.03; H, 6.92.

The red 2,4-dinitrophenylhydrazone prepared in the usual manner and recrystallized from ethyl acetate-methanol melted at 256–257°.

Anal. Calc'd for C17H16N4O5: C, 57.30; H, 4.53.

Found: C, 57.34; H, 4.76.

6-Methoxy-3,3-dimethyl-1-indanone (XII). 6-Hydroxy-3,3-dimethyl-1-indanone (20 g.) was added to 60 ml. of water containing 5 g. of sodium hydroxide and the whole was cooled to 10°. Dimethyl sulfate (11 ml.) was added dropwise over a period of approximately one-half hour. After the addition was complete the mixture was heated on the steam-bath for one hour. The mixture was cooled (an organic layer had separated) and extracted with ether. The ether layer was washed with water and dried over magnesium sulfate. After removal of the ether under reduced pressure the residue was distilled to yield 13 g. of colorless 6-methoxy-3,3-dimethyl-1-indanone, b.p. 132–135/7.5–8 mm. This material solidified on standing and was recrystallized from petroleum ether (20–40°), m.p. 32°.

Anal. Calc'd for C₁₂H₁₄O₂: C, 75.76; H, 7.42.

Found: C, 75.61; H, 7.41.

The red 2,4-dinitrophenylhydrazone prepared in the usual manner and recrystallized from toluene melted at 281-282°.

Anal. Cale'd for C₁₈H₁₈N₄O₅: C, 58.37; H, 4.90.

Found: C, 58.51; H, 5.06.

The oxime, 9 g. (compound XIII), was prepared in the usual manner using hydroxylamine hydrochloride (11 g.), pyridine (20 ml.), absolute ethanol (60 ml.), and 9 g. of the ketone (compound XII). The oxime was a solid which melted at 137-138° after recrystallization from benzene-petroleum ether (60-80°).

Anal. Cale'd for C12H15NO2: C, 70.22; H, 7.37.

Found: 70.40; H, 7.41.

6-Methoxy-3,3-dimethyl-1-aminoindan (XIV). The reduction of the above oxime was accomplished in the same manner as reported for the preparation of compound III. From 9 g. of the oxime 8 g. of the amine was obtained which boiled at $118-119^{\circ}/7 \text{ mm.}, n_{p}^{24}$ 1.5384.

Anal. Calc'd for C12H17NO: C, 75.35; H, 8.96.

Found: C, 75.36; H, 8.97.

The hydrochloride of XIV, the methoxyamine, was prepared in the manner described above and was recrystallized from absolute ethanol-ether, m.p. 246-247°.

Anal. Calc'd for C₁₂H₁₈ClNO: C, 63.28; H, 7.97.

Found: C, 63.23; H, 8.09.

6-Methoxy-3,3-dimethyl-1-dimethylaminoindan (XV). This substance was prepared in

the same manner as described for compound IV. The product (4.8 g. was obtained from 5.5 g. of compound XIV) was a liquid, b.p. $119-121^{\circ}/7$ mm.

Anal. Cale'd for C₁₄H₂₁NO: C, 76.66; H, 9.65.

Found: C, 77.01; H, 9.68.

The hydrochloride was prepared by passing dry hydrogen chloride into an ethereal solution of compound XV. This was recrystallized from absolute ethanol-ether, m.p. 139-140°. Anal. Cale'd for C₁₄H₂₂ClNO: C, 65.74; H, 8.67.

Found: C, 65.73; H, 8.70.

 β -(p-Anisoyl)isovaleric acid (XVI). A mixture of ethyl β , β -dimethylacrylate (22.5 g.) and anisole (50 g.) in carbon disulfide (100 ml.) was added dropwise to an ice-cold, stirred mixture of aluminum chloride (100 g.) in carbon disulfide (250 ml.). The mixture was stirred for six hours at ice-bath temperature and 16 hours at room temperature (three-hour stirring at ice temperature and then decomposing gave no yield). The mixture was poured with stirring onto crushed ice and hydrochloric acid and the resulting oil was extracted with ether. The ether extract was washed until neutral and dried over magnesium sulfate. After removal of the drying agent, the solution was distilled; ethyl β -(p-anisoyl)isovalerate (12.5 g. or 30%) boiled at 118-128° at 0.3 mm. The ester was hydrolyzed by refluxing for two hours with 300 ml. of 10% aqueous sodium hydroxide. The cooled mixture was extracted with ether and the aqueous alkaline mixture was acidified to give 7 g. of crude acid. After crystallization from petroleum ether (60-80°), a recrystallization from dilute alcohol produced β -(p-anisoyl)isovaleric acid melting at 86-88°.

Anal. Calc'd for C₁₂H₁₆O₈: C, 69.20; H, 7.56.

Found: C, 68.95; H, 7.56.

3,8-Dimethyl-6-methoxyindanone (XVII). The cyclization of the above acid was accomplished by the method of Johnson and Shelberg (5). A mixture of β -(p-anisoyl)isovaleric acid (3.2 g., 0.015 mole), benzene (70 ml.), and phosphorus pentachloride (3.5 g., 0.017 mole) was heated to 50-60° for one hour and then concentrated under reduced pressure (water aspirator) at 85-95°. The residue was dissolved in dry benzene (70 ml.), cooled in an icebath, and aluminum chloride (2.4 g., 0.018 mole) was added with stirring over 20 minutes. The green reaction mixture was stirred at room temperature for 3^{1} /2 hours and then decomposed with ice-hydrochloric acid. The oily product was separated with ether and the ether layer was extracted with base. The ether layer was washed, dried, and concentrated to give 2.9 g. of 3,3-dimethyl-6-methoxyindan, b.p. 113-116°/0.3 mm.

The oxime, prepared in the usual manner, was crystallized three times from methanolwater and then from benzene-petroleum ether $(90-100^\circ)$ to give white needles which melted at 105-106°. When these needles were heated to 150° and then allowed to slowly resolidify, hard rock crystals were obtained which melted at 136-138° and gave no depression with the oxime prepared earlier. This oxime isomer conversion was also brought about by dissolving the oxime in petroleum ether (60-80°) and allowing the solution to evaporate to dryness on a steam-bath.

The 2,4-dinitrophenylhydrazone, prepared in the usual manner, melted at 278-280° after recrystallization from toluene-methanol and gave no depression with that derivative prepared earlier.

SUMMARY

A series of 1-amino-3,3-dimethylindans have been prepared in which a substituent is present in the 6-position in the aromatic nucleus.

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