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Synthesis of 1-(3,5-Dimethyl-4-carbomethoxyphenyl)-2-hydrazinopropane

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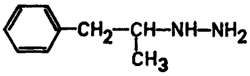
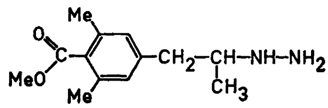
The title compound (II) and its N-acetyl derivative (III), which are structurally related to Catron® (1-phenyl-2-hydrazinopropane, I) have been synthesised.

1-Phenyl-2-hydrazinopropane (I), JB-516 or Catron®, is a drug with amphetamine-like activity and has a powerful monoamine oxidase inhibit-



I



II

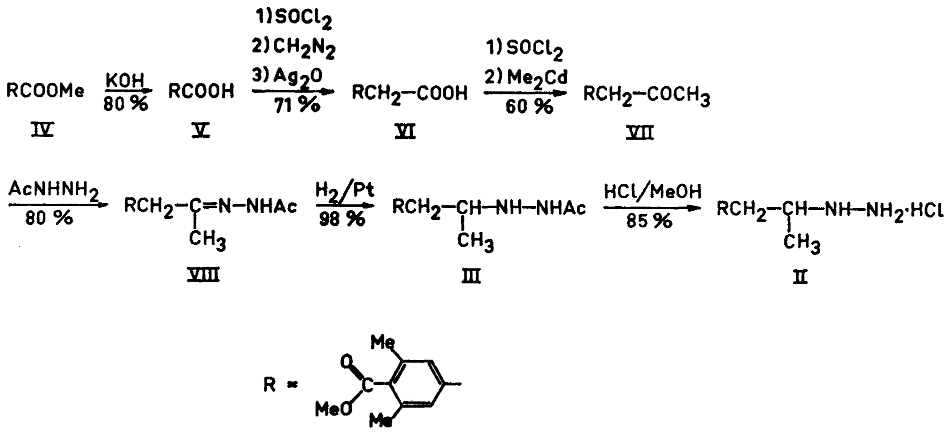
ing effect.[1–6] The present paper reports the synthesis of a related substance 1-(3,5-dimethyl-4-carbomethoxyphenyl)-2-hydrazinopropane (II) and its N-acetyl derivative (III).

The synthesis, outlined in the scheme below, started from the dimethyl ester of 2,6-dimethylterephthalic acid (IV). The non-hindered ester group was saponified and the monocarboxylic acid (V) obtained was converted by an Arndt-Eistert synthesis into the corresponding phenylacetic acid (VI). The acid chloride of VI, on treatment with dimethylcadmium, yielded the ketone VII. Treatment of V with methyllithium yielded the same ketone (VII) but in a lower yield (24 %). This low yield is consistent with an observation by Tegnér [7] that low yields are obtained in this reaction when the acid carries electron-repelling groups, assuming that the two methyl groups more than balance the carbomethoxy group. The ketone was condensed with acetylhydrazide and the hydrazone (VIII) reduced catalytically to the hydrazine derivative (III). The high yield of the reduction (98 %) is surprising. With other hydrazones, *e.g.* that of phenylacetone, side reactions such as fission

* Deceased.

on the N—N-linkage are observed, which reduce the yield considerably.[4] Finally, the N-acetyl group of III was removed by treatment with methanolic hydrochloric acid to yield II.

Pharmacological tests, carried out on the hydrochlorides show that 1-(3,5-dimethyl-4-carbomethoxyphenyl)-2-hydrazinopropane (II) has a considerably



lower monoamine oxidase inhibiting effect than Catron and that its N-acetyl derivative (III) is inactive. Both substances have blood pressure depressing action.

EXPERIMENTAL

Melting points are corrected. Melting points of hygroscopic hydrochlorides were determined in sealed capillary tubes. Evaporations were carried out under reduced pressure at a bath temperature not exceeding 50°. Distillations were performed in an atmosphere of argon. All solvents, ethyl ether, dioxane, and tetrahydrofuran were free from peroxides.

Dimethyl-2,6-dimethylterephthalate (IV). 2,6-Dimethylterephthalic acid [8] was methylated with dimethyl sulphate by the method of Cachia and Wahl.[9] The pH of the reaction was controlled with α-naphtholphthalein (pH 7.3—8.3). The crude ester, m.p. 62—67°, yield 85 %, was not further purified.

2,6-Dimethylterephthalic acid 1-monoester (V) was prepared by a modification of the procedures of Cachia and Wahl [9] and of Feist.[10] IV (275 g) was added, under vigorous stirring, to a hot (95°) solution of potassium hydroxide (77 g) in water (3.4 l). The mixture was stirred and heated to boiling which took 3 min and then boiled for 7 min, whereupon all the diester dissolved. The solution was rapidly cooled and extracted with ethyl ether. Concentration of the ether extract yielded a viscous liquid (33 g), which distilled between 73—76°/0.6 mm, n_D^{25} 1.5075. It gave a negative hydroxamate test, but was not further investigated. All hydroxamate tests in the present investigations were performed according to Feigl.[11] However, it was found that the sterically hindered ester groups present in substances II—VIII did not react under such conditions.

The aqueous phase was acidified with 4 M hydrochloric acid and the precipitate of V collected and washed with cold water. The product (206 g), m.p. 150—152°, was not further purified.

3,5-Dimethyl-4-carbomethoxyphenylacetic acid (VI). V (110 g) was converted into the acid chloride by reaction with thionyl chloride in the usual manner. The acid chloride was distilled at 163—164°/11 mm and the distillate (115 g) allowed to solidify, m.p. 65—66°. An analytical sample was prepared by recrystallisation from light petroleum. Colourless crystals, m.p. 65.5—66.5°. (Found: C 58.3; H 4.85; Cl 15.5. $C_{11}H_{11}ClO_3$ requires: C 58.3; H 4.89; Cl 15.7).

The acid chloride (61 g) was treated with diazomethane (26.1 g) in anhydrous ethyl ether (1.3 l), following the general procedure for the synthesis of diazoketones.[12] Crystallisation of the product at −35° gave yellow crystals (49 g), m.p. 120—122° (decomp.) which were collected and washed with dry, cool ether. An analytical sample, m.p. 121—122°, was prepared by recrystallisation from methanol. (Found: C 62.1; H 5.22; N 12.0. $C_{12}H_{12}N_2O_3$ requires: C 62.1; H 5.21; N 12.1).

The diazoketone (69 g) in peroxide-free dioxane (600 ml) was added dropwise during 1 h to a stirred suspension of silver oxide (78 g) in 0.22 M aqueous sodium thiosulphate (3.8 l) at 65°. (It seems to be essential that the dioxane is peroxide-free, otherwise inferior yields are obtained). Stirring was continued for 1 h.

Norit (3 g) was added and the mixture cooled and filtered. The filtrate was acidified with 4 M hydrochloric acid and the precipitate obtained was collected and dissolved in ethyl ether (600 ml). The filtrate was extracted with ether (5 × 200 ml) and the combined ether solutions were washed with water (2 × 100 ml), dried over magnesium sulphate, filtered, and the solvents evaporated. The remaining powder was dispersed in water (100 ml), filtered off, and washed with water. The product (63 g) melted at 93—95°. An analytical sample, m.p. 95.5—96°, was obtained as colourless crystals by recrystallisation from cyclohexane. (Found: C 65.1; H 6.46. $C_{12}H_{14}O_2$ requires: C 64.9; H 6.35).

3,5-Dimethyl-4-carbomethoxyphenylacetone (VII). VI (31 g) was converted into the acid chloride (33 g) by reaction with thionyl chloride in the usual manner. The acid chloride distilled at 140—142°/0.8 mm, n_D^{25} 1.5270. Part of the product was redistilled at 127—128°/0.2 mm, n_D^{25} 1.5265. (Found: C 59.9; H 5.40; Cl 15.0. $C_{12}H_{13}ClO_3$ requires: C 59.9; H 5.44; Cl 14.7).

The acid chloride (9.5 g) was treated with dimethylcadmium according to the procedure of Cason[13] ("method A. Benzene as Solvent"). The crude ketone (5.4 g), b.p. 131—133°/0.6 mm, n_D^{25} 1.5158, contained some diester (positive hydroxamate test). Since the keto groups are supposed to react much more rapidly than the ester groups, in the subsequent reactions with acetylhydrazide, further purification was not considered necessary.

An analytical sample of VII was prepared by alkaline treatment of the crude product, to saponify the non-hindered ester group of the diester impurity. Purified VII, which gave a negative hydroxamate test, distilled at 116—117°/0.2 mm, n_D^{25} 1.5158, and gave a blue fluorescence under UV. (Found: C 70.8; H 7.66. $C_{13}H_{16}O_3$ requires: C 70.9; H 7.32).

The ketone VII was also prepared from the acid VI by reaction with methyllithium, as described by Tegnér.[7] The yield of VII was 24 % and in addition, starting material (52 %) was recovered. This method for preparation of VII is thus inferior to the longer route, described above.

The 2,4-dinitrophenylhydrazone of VII was prepared, m.p. 179—181°. (Found: C 57.5; H 5.06; N 14.1. $C_{19}H_{20}N_4O_6$ requires: C 57.0; H 5.04; N 14.1).

1-Acetyl-2-(3,5-dimethyl-4-carbomethoxyphenylisopropyliden)hydrazine (VIII). A solution of VII (4.60 g) and acetyl hydrazide (1.60 g) in anhydrous ethanol (6 ml) was refluxed for 5 min and then kept at room temperature overnight. The colourless crystals were collected and washed successively with cold ether, water, and cold ether again. The product (4.60 g) melted at 150—151°. Further material (0.10 g), with the same m.p., was obtained from the mother liquor. An analytical sample, m.p. 151—151.5° was prepared by recrystallisation from propanol-water. (Found: C 65.6; H 7.40; N 10.2. $C_{15}H_{20}N_2O_3$ requires: C 65.2; H 7.30; N 10.1).

1-Acetyl-2-[β-(3,5-dimethyl-4-carbomethoxyphenyl)-isopropyl]hydrazine (III). A solution of VIII (13.5 g) in anhydrous ethanol (115 ml) and acetic acid (115 ml) was hydrogenated at atmospheric pressure and room temperature in the presence of Adams' catalyst (0.2 g). The consumption of hydrogen (1180 ml) was complete within 90 min. The filtered solution was concentrated to 25 ml, water (25 ml) was added and the base precipitated by addition of 2 M sodium hydroxide. The crystalline product (13.5 g), m.p. 115.5—116.5°, was collected and washed with cold water. An analytical sample, m.p. 116.5—117.5°, was prepared by crystallisation from propanol-water. (Found: C 64.9; H 8.11; N 10.0. $C_{15}H_{22}N_2O_3$ requires: C 64.7; H 7.97; N 10.1).

The hydrochloride of III was prepared by dissolving III (2.0 g) in tetrahydrofuran (10 ml) and adding 1.7 M ethereal hydrogen chloride (5 ml), followed by ether (30 ml). The crude product (2.2 g) had a m.p. 179—182° (m.p. 180—182° (decomp.) after recrystallisation from tetrahydrofuran-ether). (Found: Cl 11.3. $C_{15}H_{23}ClN_2O_3$ requires: Cl 11.3).

1-(3,5-Dimethyl-4-carbomethoxyphenyl)-2-hydrazinopropane hydrochloride (II). A mixture of III (6.0 g) and conc. hydrochloric acid (15 ml) in methanol (90 ml) was stirred under reflux for 3 h. The solution was evaporated to dryness under argon and the residue suspended in ether (100 ml), filtered and dried *in vacuo* over potassium hydroxide and silica gel. Recrystallisation from tetrahydrofuran yielded the pure substance (5.0 g), m.p. 175—176° (decomp.) as colourless needles. (Found: C 57.1; H 7.62; Cl 13.2; N 10.2. $C_{13}H_{21}ClN_2O_2$ requires: C 57.2; H 7.76; Cl 13.0; N 10.3).

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