26. 6-*Aminoacetoveratrone and* 5 : 6-*Dimethoxy*-3-*methylanthranil.*

By J. C. E. Simpson.

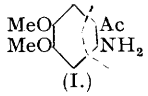
According to conditions of reduction, 6-nitroacetoveratrone is converted into either of two substances, m. p. 133° and 108°, or into a mixture of both these products. Each of these compounds has been designated as 6-aminoacetoveratrone (I), the former by Lawson, Perkin, and Robinson (*J.*, 1924, **125**, 626), and the latter by

Mannich and Berger (*Arch. Pharm.*, 1939, **277**, 117); the German authors regard the substance, m. p. 133°, as the anthranil (III).

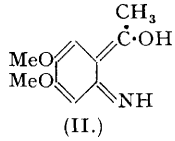
Experiments are described which indicate that the conclusions of Mannich and Berger are correct.*

DURING a review of existing *o*-aminoacetophenones (*J.*, 1945, 646), a study was made of the preparation and properties of the substance, m. p. **133°**, prepared by Lawson, Perkin, and Robinson (*loc. cit.*) by reduction of 6-nitroacetoveratrone and designated 6-aminoacetoveratrone (I) by these authors.

The best method for the preparation of acetoveratrone appears to be that of Koepfli and Perkin (*J.*, 1928, 2989); substitution of acetic anhydride for acetyl chloride, which Noller and Adams (*J. Amer. Chem. Soc.*, 1924, **46**, 1889) have shown usually effects a marked improvement in the preparation of substituted acetophenones, gave inferior yields in this case. Nitration of the ketone to 6-nitroacetoveratrone was, surprisingly, always unsatisfactory under the conditions of Lawson, Perkin, and Robinson (*loc. cit.*) [substantially the same conditions are also described by Mannich and Berger (*loc. cit.*)], but consistently high yields were obtained by slightly modifying these conditions. For the reduction of the nitro-ketone, these authors used a stoicheiometric deficiency of stannous chloride, but made no mention of unchanged nitro-compound, which, in a repetition of their work, was always found to be present with the substance, m. p. **133°**. When stannous chloride was employed in excess, no unchanged nitro-compound was isolated, the products of the reaction being the compound, m. p. **133°**, and a second substance, m. p. 106—108°, analysis of which indicated an empirical formula $C_{10}H_{13}O_3N$. This substance gave an acetyl derivative, m. p. 128°, from which it could be regenerated by acid hydrolysis; it was formed as the sole isolable product when 6-nitroacetoveratrone was reduced by West's method (*J.*, 1925, **127**, 494) or with iron and acetic acid.



(I.)



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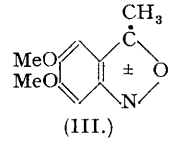

(III.)

6-Nitroacetoveratrone forms an anisylidene derivative (Lawson, Perkin, and Robinson, *loc. cit.*), and a *furfurylidene* derivative was similarly produced in presence of alcoholic potassium hydroxide; piperidine failed to effect condensation with anisaldehyde. The reduction product, m. p. **133°**, on the other hand, failed to give either a chalkone or a Schiff base with anisaldehyde under alkaline conditions (piperidine or potassium hydroxide), and it resisted acetylation under normal conditions. The assumption that the portion of the molecule indicated by the broken line in (I) might function as a "vinylogue" of a neutralised system [Robinson, "Outline of an Electrochemical (Electronic) Theory of Organic Reactions," 1932, p. 27], $C(NH_2):C\cdot CO$, is not an explanation of this lack of reactivity, because *o*-aminoacetophenone has long been known to acetylate normally (Baeyer and Bloem, *Ber.*, 1882, **15**, 2147)—the reaction is in fact appreciably exothermic—and Mannich and Dannehl (*Ber.*, 1938, **71**, 1899) have prepared 2-aminochalkone from *o*-aminoacetophenone and benzaldehyde. [Incidentally, these authors do not comment on the fact that their aminochalkone, m. p. 71°, is different from the substance, m. p. 147°, to which the same constitution was previously ascribed by Engler and Dorant (*Ber.*, 1895, **28**, 2497); the discrepancy is possibly explained by geometrical isomerism, as the substances were prepared by different methods.] A feasible structure for the substance, m. p. **133°**, appeared to be (II), arising from (I) by tautomeric change (theoretical considerations suggest that this could readily occur), and this structure received superficial support from the observation that 80% of the substance, m. p. **133°**, was recovered from reaction with excess of ethylmagnesium bromide under "inverse" conditions at room temperature [a resinous product was formed when the substance in ether was added to a large excess of alkylmagnesium halide under reflux; β-(2-amino-4 : 5-dimethoxybenzoyl)-propionic acid and its ethyl ester (Schofield and Simpson, *J.*, 1945, 520) also gave non-crystalline products when added to a large excess of methylmagnesium iodide]. The compound also reacted with maleic anhydride in boiling xylene, but not in boiling benzene; the product of this reaction was a dark resin, which gave an amorphous acid on hydrolysis.

An alternative suggestion as to the structure of the compound, m. p. **133°**, has been made by Mannich and Berger (*loc. cit.*). They regard this substance as the anthranil (III),† and assign the constitution (I) to a compound, m. p. 107°, which they obtained as the sole product of the catalytic reduction of 6-nitroacetoveratrone. As Mannich and Berger's compound, m. p. 107°, gave analytical figures in agreement with the formula $C_{10}H_{13}O_3N$, and yielded an acetyl derivative, m. p. 127·5°, there can be no doubt that the substance is identical with the compound, m. p. 106—108°, prepared during the present work by reduction of 6-nitroacetoveratrone, but under different conditions.

Mannich and Berger's assignment of structures (III) and (I) to the compounds, m. p. 133° and 107°, is based, in addition to analytical data, on statements that the former may be reduced to the latter, and that the corresponding indigo derivative was obtained from the acetamido-compound, m. p. 127·5°, *via* the ω-bromo-

* Sir Robert Robinson has kindly informed the author that results of work in his laboratory subsequent to the original publication are in agreement with the conclusions reached in this paper. The amount of stannous chloride used was much greater than stated and the product, as shown *inter alia* by the reactions cited, was largely the amino-ketone. Crystallisation afforded a relatively small yield of the substance, m. p. 133°.

† The modified formula (III) is suggested as a convenient symbol for giving expression to the considerations outlined by Baker (*J.*, 1945, 267) respecting the structure of such substances.

derivative. However, these authors have not recorded experimental support for these statements, and independent evidence to settle the point was therefore sought.

That the substance, m. p. 107°, is correctly formulated as (I) was demonstrated by nitration of the *N*-acetyl derivative, m. p. 128°; this led to elimination of the *C*-acetyl group with formation of 4-nitro-5-acetamidoveratrole (for examples of the elimination of carboxyl or *C*-acetyl groups during nitration, see Harding, *J.*, 1911, 1585; 1914, 2790; Simonsen *et al.*, *J.*, 1917, 71; 1918, 22; Lawson, Perkin, and Robinson, *loc. cit.*, p. 653). It was also found that the substance, m. p. 133°, is converted, like 6-nitroacetoveratrone, into 6-aminoacetoveratrone by treatment with iron and acetic acid, and that it yielded a mixture of the aminoketone and the *oxime* of the latter on treatment with hydroxylamine; it is therefore an intermediate stage in the reduction of the nitro- to the amino-ketone, and is thus correctly formulated, in accord with the statement of Mannich and Berger, as the anthranil (III).

Experimental.

(M. p.'s are uncorrected.)

6-Nitroacetoveratrone.—Application of the general method of Noller and Adams to the preparation of acetoveratrone was unsatisfactory; from veratrole (70 g.) and acetic anhydride (55 g.) the former (28 g.) was recovered, and the ketone (26·5 g.) isolated represented a yield of 48% based on reacted veratrole. The use of nitrobenzene as solvent gave variable results, the best being a 51% yield with no recovery of veratrole. Acetoveratrone invariably had b. p. 168—169°/14 mm., in agreement with the value found by Koepfli and Perkin (b. p. 160—162°/10 mm., *loc. cit.*); the figures given in Heilbron's "Dictionary of Organic Compounds" (1st. Edition) and by Pictet and Gams (*Ber.*, 1909, **42**, 2947) are evidently erroneous (205—207°/10—15 mm. and 206°/12 mm. respectively). In the literature method for the nitration of acetoveratrone, nitric acid (*d* 1·42) alone was used as the nitrating agent; the best result obtained in several repetitions of the method was 4·6 g. of nitro-ketone from 10 g. of acetoveratrone. The following conditions gave an 86% yield of recrystallised product. Powdered acetoveratrone (13·5 g.) was added in portions during 10—12 minutes to a mechanically-stirred mixture of nitric acid (47 c.c., *d* 1·42) and concentrated sulphuric acid (20 c.c.), the reaction temperature being kept between −5° and −3°. The nitro-ketone usually (but not always) began to crystallise after the last of the ketone had been added, and after ½ hour the mass was poured into water and recrystallised from alcohol (14·5 g., m. p. 133·5—135°).

The furfurylidene derivative was prepared by warming a mixture of the ketone (5 g.), furfural (3·5 c.c.), and alcohol (50 c.c.) until most of the solid had dissolved. Addition of aqueous potassium hydroxide (1 c.c., 30%) produced much evolution of heat, and a crystalline mass separated. After washing with cold alcohol, almost pure *furfurylidene derivative* (5·85 g., 87%) was obtained, very sparingly soluble in alcohol, and separating from aqueous acetic acid in long pale yellow needles, m. p. 150—151° (Found: C, 59·4; H, 4·7; N, 5·1. $C_{15}H_{13}O_6N$ requires C, 59·4; H, 4·3; N, 4·6%).

The anisylidene derivative (yield, 79%) formed small lemon-yellow needles, m. p. 168—169°, from aqueous acetic acid (Lawson, Perkin, and Robinson, *loc. cit.*, give m. p. 170°) (Found: C, 62·95; H, 5·05. Calc. for $C_{18}H_{17}O_6N$: C, 63·0; H, 5·0%). No reaction between the ketone and anisaldehyde occurred in hot alcoholic solution when piperidine was used in place of potassium hydroxide.

Reduction Experiments with 6-Nitroacetoveratrone.—(a) Reduction by the stannous chloride method of Lawson, Perkin, and Robinson (*loc. cit.*) was incomplete; 5 g. of ketone gave unchanged material (1·65 g.) and the anthranil (1·85 g.). Replacement of half of the hydrochloric acid by the same volume of glacial acetic acid had little effect on the yield (1 g. of nitro-compound recovered and 1·8 g. of anthranil). (b) Using excess stannous chloride, 6-aminoacetoveratrone was formed. A finely-divided suspension of the nitro-ketone (5 g.) in acetic acid (25 c.c.) was treated with a solution of stannous chloride (22 g.) in concentrated hydrochloric acid (28 c.c.). After an hour, fine colourless needles separated on scratching; this material was collected after a further 2 hours and yielded anthranil [1·85 g., m. p. 131—132·5° alone and mixed with authentic material prepared by method (a)] after decomposition with alkali and recrystallisation from methanol. A sample prepared for analysis from aqueous alcohol formed small, almost colourless prisms, m. p. 133—134° [Found: C, 61·8; H, 5·5. Calc. for $C_{10}H_{11}O_3N$ (anthranil): C, 62·15; H, 5·75. Calc. for $C_{10}H_{13}O_3N$ (amino-ketone): C, 61·5; H, 6·7%]. The filtrate from the stannichloride was treated with excess potassium hydroxide and extracted with ether until the extracts were colourless. The ethereal solution was washed twice with a little water, dried and evaporated, yielding crude crystalline material (1 g.); this was very soluble in alcohol, easily so in hot water, and considerably less so in ether. After crystallisation from ether containing a little alcohol and finally from ether alone, 6-aminoacetoveratrone separated in very pale yellow, slender, dull needles, m. p. 106—108° (depressed when mixed with either the nitro-ketone or the anthranil) (Found: C, 61·1; H, 6·7; N, 7·6. Calc. for $C_{10}H_{13}O_3N$: C, 61·5; H, 6·7; N, 7·2%). When heated with acetic anhydride (10 c.c.) at 95° for 1½ hours, the amine (4 g.) gave the acetyl derivative (3·8 g.); this substance was very soluble in alcohol and hot water, and formed fine, colourless, woolly needles, m. p. 127—128°, from benzene–ligroin (b. p. 60—80°) (Found: C, 61·45; H, 6·5; N, 6·3. Calc. for $C_{12}H_{15}O_4N$: C, 60·75; H, 6·4; N, 5·9%). It was reconverted into the amine by heating for 1 hour at 100° with a mixture of concentrated (10 parts) and 2N-hydrochloric acid (20 parts); after addition of ammonia and crystallisation from aqueous methanol, the base had m. p. and mixed m. p. 106—108°. (c) A boiling solution of 6-nitroacetoveratrone (2·25 g.) in methylated spirit (15 c.c.) and concentrated hydrochloric acid (0·5 c.c.) was treated with iron filings (2 g., added in 4 portions at 5-minute intervals). After being refluxed for 2½ hours, the suspension was made alkaline with aqueous sodium hydroxide and extracted 5 times with ether. The washed and dried extracts, on evaporation, gave a residue which furnished the amine (1·5 g.) from ether containing a little benzene; m. p. and mixed m. p. 106—107° after recrystallisation (Found: C, 60·8; H, 6·9; N, 7·4%). (d) The nitro-ketone (5 g.) in acetic acid (40 c.c.) was treated on the steam-bath with iron filings (7·5 g.), added in portions during 1 hour with frequent shaking; additions of 10 c.c. portions of water were made at the start of the reaction and after ¾ hour. After a total of 1½ hours, the mixture was diluted with water and the product isolated by ether-extraction, yielding once crystallised material (3·2 g.), m. p. 103—105° (identified by mixed m. p.).

Oxime of 6-Aminoacetoveratrone.—Prepared from the ketone (1 part), hydroxylamine hydrochloride (1·5 parts), and fused sodium acetate (2 parts) in boiling aqueous alcoholic solution, the *oxime* was obtained in fine colourless needles, m. p. 154·5—156° after crystallisation from hot water (Found: C, 56·95; H, 6·4; N, 13·55. $C_{10}H_{14}O_3N_2$ requires C, 57·1; H, 6·7; N, 13·3%).

Experiments with 5 : 6-Dimethoxy-3-methylanthranil.—(a) From attempts to condense the substance with anisaldehyde in presence of either piperidine or potassium hydroxide in alcohol, unchanged material (the only isolable product) was recovered to the extent of 45—60%. (b) A solution of the substance (0·6 g.), hydroxylamine hydrochloride (0·9 g.), and fused sodium acetate (1·2 g.) in 50% aqueous alcohol (12 c.c.) was refluxed for 1½ hours; solvent was then removed in an evacuated desiccator until crystallisation occurred. The crude oxime of 6-aminoacetoveratrone (0·35 g.) was crystallised several times from hot water, from which it separated in soft colourless needles, m. p. 154—155·5°, not depressed on mixing with the specimen described above. The original filtrate on further concentration gave 0·3 g. of easily-soluble material. From this, some of the foregoing oxime was removed by crystallisation from a little water;

the material in the filtrate was then isolated and crystallised from ether–ligroin (b. p. 40—60°), giving pale yellow needles, m. p. 105—107° alone and mixed with 6-aminoacetoveratrone (Found: C, 61·5; H, 6·4; N, 7·5%). (c) The product obtained by reduction at 85° of the anthranil (0·5 g.) in acetic acid (5 c.c.) with iron powder (0·7 g.) [water (6 c.c.) was added in portions during the reaction] was isolated by dilution with water and extraction with chloroform. The residue from the washed, dried, and evaporated extract was taken up in ether and yielded the amino-ketone (0·25 g.), m. p. and mixed m. p. 106—107°. (d) The anthranil (300 mg.) and maleic anhydride (300 mg.) were heated with xylene (3 c.c.) (cf. Schönberg and Mostafa, *J.*, 1943, 654); a dark solution was formed, followed by gradual deposition of a dark resinous solid. After 3 hours' refluxing and leaving the mixture for 48 hours, the xylene was decanted from the resin and crystalline matter which had separated. The whole residue was heated at 95° for 1 hour with 2N-aqueous sodium hydroxide, and then extracted with ether. The extract gave unchanged anthranil (50 mg.) and the alkaline solution, on acidification, yielded a dark amorphous solid (130 mg.), m. p. 240—260° (decomp.), easily soluble in glacial acetic acid, and separating in amorphous form on gradual dilution with water.

Nitration of 6-Acetamidoacetoveratrone.—The acetamido-ketone (1·5 g.) was added during 12 minutes to 10 c.c. of a mixture of nitric acid (10 c.c., *d* 1·42), acetic acid (4 c.c.), and water (2 c.c.) at a temperature not exceeding −10°; crystallisation of the product set in after about half the material had been added. After 18 minutes from the start of the experiment, the paste was poured on to ice, and the solid recrystallised from alcohol, yielding soft golden needles (1·25 g.) of 4-nitro-5-acetamidoveratrole, m. p. 196—197° [lit. m. p.'s, 196° (Simonsen and Rau, *J.*, 1918, 22); 199° (Jones and Robinson, *J.*, 1917, 903)]. Hydrolysis with a mixture of equal volumes of alcohol, water, and concentrated hydrochloric acid (boiled for ½ hour) gave 4-nitro-5-aminoveratrole, which separated from alcohol in orange-red needles, m. p. 173—174° (Found: N, 14·6. Calc. for $C_8H_{10}O_4N_2$: N, 14·1%). Simonsen and Rau, *loc. cit.*, give m. p. 171°, and Jones and Robinson, *loc. cit.*, record m. p. 175°.

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