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THE NITRATION OF SOME METHYL SUBSTITUTED INDOLE-3-ALDEHYDES IN SULPHURIC ACID

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Abstract—The nitration of 1-methylindole-3-aldehyde, 2-methylindole-3-aldehyde and 1,2-dimethylindole-3-aldehyde in sulphuric acid gives in ca. 92% yield mixtures of the corresponding 5- and 6-nitro derivatives. These mixtures contain a small excess of the 5-nitro derivatives. The occurrence of various side-reactions, which complicated the course of the nitration when acetic acid was used as solvent, was not observed in this case.

IN A previous paper,[1] dealing with the nitration of some methyl substituted indole-3-aldehydes in acetic acid, it was shown that the presence of a methyl group in the 1-position results in substantial destabilization of the molecule, as evidenced by the isolation of a number of side-products from the reaction mixture, while the presence of a methyl group in the 2-position stabilizes the indole system towards oxidation, thus leading to better yields of nitro derivatives. Since indole derivatives have been shown in many instances[2] to respond quite differently to electrophilic reagents, depending on whether the molecule is protonated (sulphuric acid medium) or not (acetic acid medium), it was decided to investigate the nitration of the same indole-3-aldehydes in sulphuric acid solution.

Nitration of 1-methylindole-3-aldehyde (I, Chart I) with potassium nitrate in concentrated sulphuric acid gave a 93% yield of a mixture of two mononitro compounds, which could be partially separated by fractional crystallization, and were identified as 1-methyl-5-nitroindole-3-aldehyde (IIa, 60% of the mixture) and 1-methyl-6-nitroindole-3-aldehyde (IIb, 40% of the mixture). Identification of IIa followed from direct synthesis by methylation of the known compound V.[2a] The qualitative and quantitative composition of the nitration mixture was further defined as follows: (a) peroxyacetic acid oxidation led to a mixture of the known N-methylnitroanthranilic acids (IIIa and IIIb) these were transformed into their methyl esters (IVa and IVb) which could be separated by chromatography over alumina; (b) UV and IR analysis proved that no other component beyond IIa and IIb was present, and allowed estimation of their relative amounts.

Nitration of 1,2-dimethylindole-3-aldehyde (VI) under the same conditions led also to a mixture (91% yield) of two mononitro derivatives (VIIa, 57%; and VIIb, 43%). Fractional crystallization allowed separation of a small amount of 1,2-dimethyl-6-nitroindole-3-aldehyde (VIIb), whose structure was proved by synthesis from the known compound (X).[1] The structure of 1,2-dimethyl-5-nitroindole-3-aldehyde (VIIa) was assigned to the other component of the mixture, on the basis of

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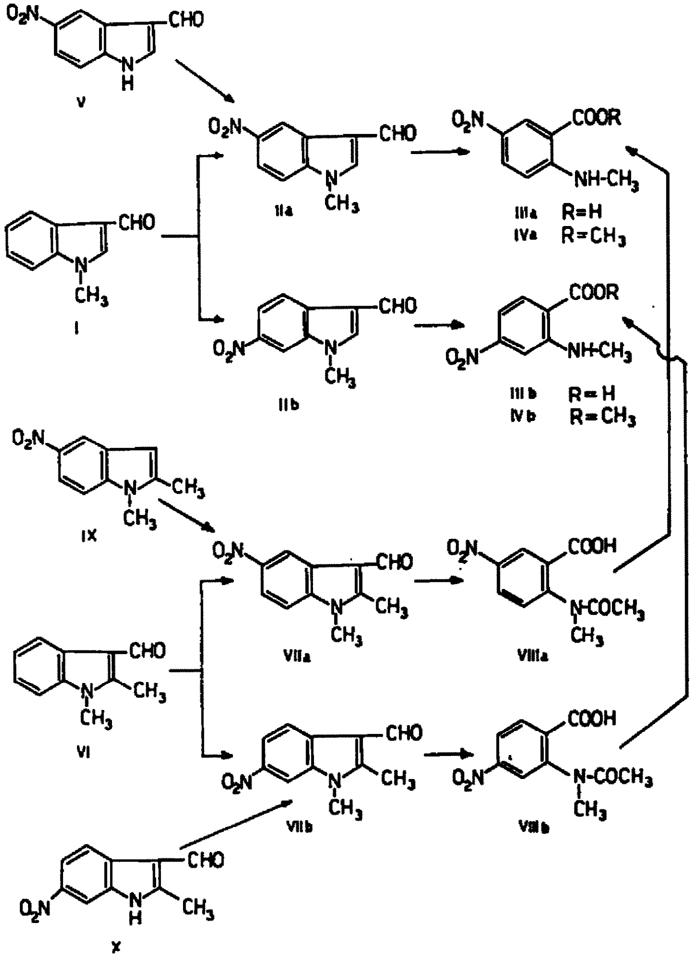
[1] G. Berti, A. Da Settimo and O. Livi, *Tetrahedron* **20**, 1397 (1964).

[2a] G. Berti and A. Da Settimo, *Gazz. Chim. Ital.* **91**, 728 (1961); [b] W. E. Noland, L. R. Smith and D. C. Johnson, *J. Org. Chem.* **28**, 2262 (1963); [c] A. Da Settimo and M. F. Saettone, *Tetrahedron* **21**, 823 (1965).

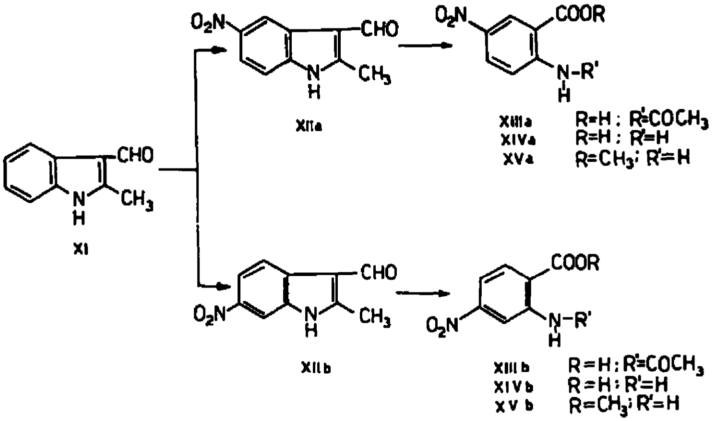
CHART I



the following considerations: (a) the IR spectrum of the mixture was identical with the spectrum of a mixture of VIIa, prepared by formylation of the known compound (IX),[2b] and VIIb; (b) peroxyacetic acid oxidation of the nitration mixture led, through the compounds VIIIa-VIIIb and IIIa-IIIb, to the same couple of methyl N-methyl-nitroanthranilates IVa and IVb, already obtained from IIa and IIb.

Similar results were obtained with 2-methylindole-3-aldehyde (XI, Chart II): nitration of this compound with potassium nitrate in sulphuric acid gave a 92% yield of a mixture of the 5- (XIIa, 58%) and 6- (XIIb, 42%) nitro derivatives. Fractional crystallization of the mixture allowed separation of XIIa; this was identified by oxidation to the known N-acetyl-5-nitroanthranilic acid (XIIIa). The composition of the nitration mixture was determined, as in the previous cases, by comparison of its IR spectrum with a spectrum of an artificial mixture of XIIa and XIIb, and by oxidation to a mixture of N-acetyl-4- (and 5-) nitroanthranilic acids (XIIIa and XIIIb). These were saponified to XIVa and XIVb, which were transformed into the corresponding methyl esters (XVa and XVb). Identification of XVa and XVb followed their separation by chromatography over alumina.

CHART II



The yields of nitro derivatives from the nitrations of either I, VI or XI could be estimated from the UV spectra of the mixtures and of the individual components. The methyl substituted 5-nitroindole-3-aldehydes all have very similar spectra (Fig. 1), which are significantly different from the spectra of the 6-nitro derivatives (Fig. 2). The UV and IR analyses also demonstrated the absence of any other nitration or side-reaction product.

An interesting outcome of this study is the observation that protonation of methyl substituted indole-3-aldehydes, as in XVI, results in significant stabilization of the molecule against oxidative attack and exchange of the formyl with the nitro group.

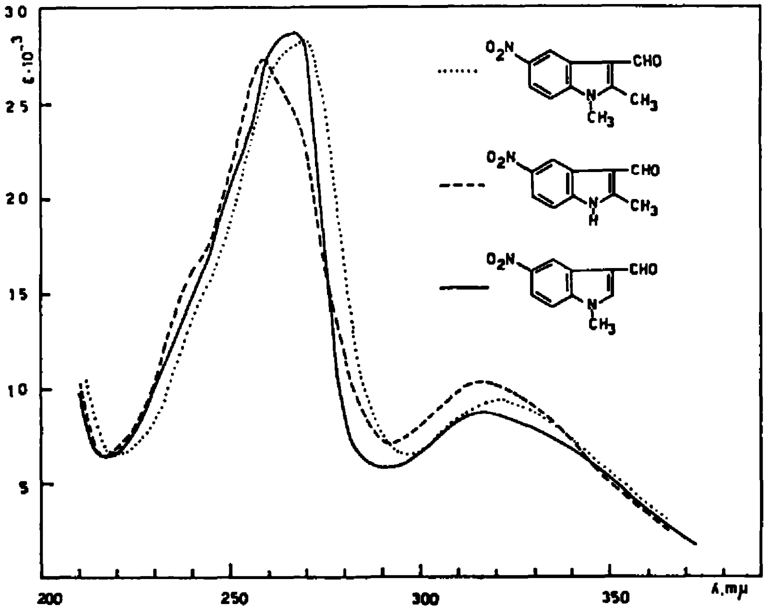


Fig. 1

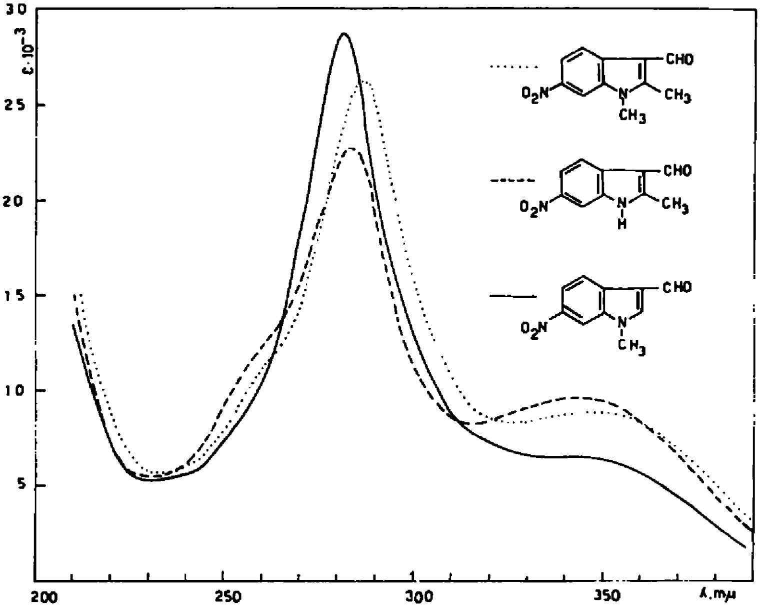
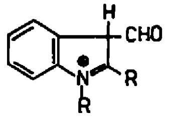


Fig. 2

This is in agreement with previous findings[2a] concerning the nitration of the unsubstituted indole-3-aldehyde: sulphuric acid nitration of this compound gave in 85% yield a mixture of the 5- and 6-nitro derivatives (66 and 34%), while a 16% yield of the 6-nitro derivative, along with substantial amounts of unidentified by-products,



XVI

resulted from acetic acid nitration. It can be clearly seen that protonation of the molecule of indole-3-aldehyde results in stabilization, which is independent of the position (or the presence) of methyl substituents; on the other hand these substituents may significantly affect the stability of the unprotonated molecule, depending on their presence and location.

EXPERIMENTAL[3]

Nitration of *1-methylindole-3-aldehyde* (I). To a solution of I[4] (1·0 g) in 9 ml of conc. H_2SO_4 was added dropwise a solution of KNO_3 (0·76 g) in 5 ml conc. H_2SO_4, while cooling in a salt-ice bath. The mixture was allowed to stand 12 min at room temp, then was poured onto crushed ice. The

[3] M.ps (Kofler apparatus) are uncorrected. IR spectra were recorded on a Perkin-Elmer Infracord Model 137 spectrophotometer, in Nujol mulls. UV spectra were obtained using a Beckman Model DU spectrophotometer. Microanalyses were performed by Alfred Bernhardt Microanalytical Laboratory, Mulheim, Germany, and by the Microanalytical Laboratory of the University of Padova, Italy. Pet. ether refers to the fraction of boiling range 40–60°. Identity of compounds was proved by mixture m.ps and comparison of IR spectra.

[4] Prepared in 89% yield by formylation of 1-methylindole, following the procedure given by P. N. James and H. R. Snyder, Organic Synthesis Vol. 39, 30 (1959), for the preparation of indole-3-aldehyde. The product (m.p. 69–70°) was identical with a sample prepared according to V. M. Rodionov and T. K. Veselovskaya, *Zh. Obsh Khim.* **20**, 2202 (1950).

yellow precipitate was collected, thoroughly washed with water and dried (1·20 g, 93%; m.p. 145–165°). Fractional crystallization of this material from benzene allowed separation of 180 mg of the less soluble 1-*methyl*-5-*nitroindole*-3-*aldehyde* (IIa) as yellow prisms, m.p. 198–200° after recrystallization from EtOH; $\lambda_{\max}^{\mathrm{EtOH}}$ (log ε) 267 (4·46), 318 (3·93) mμ; IR 6·01(s), 6·60(m), 7·49(s), 7·62(m), 9·10(m), 9·52(w), 9·75(w), 11·12(w), 11·30(w), 12·10(w), 12·63(m), 13·47(m) μ. (Found: C, 58·98; H, 4·24; N, 13·72. $C_{10}H_8N_2O_3$ requires: C, 58·82; H, 3·95; N, 13·72%).

Concentration of the mother liquors of IIa yielded, after several mixed fractions, 0·10 g of a compound which melted at 203–205° after recrystallization from EtOH; $\lambda_{\max}^{\mathrm{EtOH}}$ (log ε) 281 (4·46), 332 (infl.) mμ. This was identified, by comparison with an authentic sample,[1] as 1-*methyl*-6-*nitroindole*-3-*aldehyde* (IIb). IR and UV analysis showed the mixture to be composed of 60% IIa and 40% IIb. Several attempts to separate these compounds by chromatography over alumina were unsuccessful.

1-*Methyl*-5-*nitroindole*-3-*aldehyde* (IIa). Proof of the structure of this compound could be obtained by the following preparation. To a suspension of 5-nitroindole-3-aldehyde[5] (0·07 g) in 2 ml of 10% NaOH aq, was added slowly, with stirring, 0·3 g of dimethyl sulphate. The mixture was stirred 4 hr at room temp and filtered. The residue was washed with 10% NaOH aq, water, and dried. Recrystallization from EtOH afforded pure IIa (0·04 g), identical with the previously obtained material.

Degradation of the mixture of IIa *and* IIb. A suspension of the crude nitration mixture (1·0 g) in glacial acetic acid (20 ml) and 30% H_2O_2 (4·2 ml) was allowed to stand 8 days at room temp, with occasional swirling. A yellow precipitate (0·115 g, m.p. 271–273°), was then filtered, and identified as pure N-*methyl*-5-*nitroanthranilic acid* (IIIa) by comparison with an authentic sample.[6] The filtrate from IIIa was evaporated under red. press., and the residue was extracted with 15 ml 2N Na_2CO_3. Acidification of the alkaline extract yielded 0·4 g of a product, which was purified by sublimation at 200°/3 mm. This material, m.p. 226–245° dec, was shown by its IR spectrum to be composed of IIIa and of N-*methyl*-4-*nitroanthranilic acid*[7] (IIIb), and could not be resolved into its components by chromatography.

A solution of the mixture of pure IIIa and IIIb (0·1 g) in abs. MeOH (15 ml) was saturated with dry HCl. Evaporation of the solution gave a residue, which was thoroughly washed with 10% Na_2CO_3 aq, water, and dried (0·065 g). This material was chromatographed through a 1·4 × 30 cm column of neutral alumina, using a 1:1 benzene–pet. ether mixture as eluant, to give 20 mg of *methyl* N-*methyl*-4-*nitroanthranilate* (IVb), m.p. 124–126° (lit.[7] m.p. 124–125°). Further elution with benzene yielded 40 mg of *methyl* N-*methyl*-5-*nitroanthranilate* (IVa), m.p. 144–145°, also independently prepared by esterification of IIIa with MeOH–HCl. (Found IVa: C, 51·53; H, 4·97. $C_9H_{10}N_2O_4$ requires: C, 51·42; H, 4·80%).

Nitration of 1,2-*dimethylindole*-3-*aldehyde* (VI). To a solution of VI[8] (2·0 g) in conc. H_2SO_4 (18 ml) was added dropwise a solution of KNO_3 (1·17 g) in conc. H_2SO_4 (10 ml), while cooling in a salt-ice bath. After the addition, the mixture was allowed to stand 12 min at room temp, then was poured onto crushed ice. The yellow precipitate was filtered, washed with water, and dried (2·3 g, 91%; m.p. 177–202°) IR and UV analysis showed this material to be a mixture of 1,2-*dimethyl*-5-*nitroindole*-3-*aldehyde* (VIIa, 57%) and 1,2-*dimethyl*-6-*nitroindole*-3-*aldehyde* (VIIb, 43%). Several attempts to separate these compounds by chromatography over alumina were unsuccessful. Extraction of the mixture with hot benzene, and repeated crystallization of the undissolved residue from acetone afforded a small amount of pure VIIb as yellow needles, m.p. 246–248°, $\lambda_{\max}^{\mathrm{EtOH}}$ (log ε) 286 (4·42), 348 (3·95) mμ; IR 6·08(s), 6·56(s), 6·80(s), 7·48(s), 8·82(m), 9·20(m), 11·40(m), 11·90(w), 12·57(m), 13·50(m) μ. (Found: C, 60·26; H, 4·59; N, 13·02. $C_{11}H_{10}N_2O_3$ requires: C, 60·54; H, 4·62; N, 12·84%).

1,2-*Dimethyl*-5-*nitroindole*-3-*aldehyde* (VIIa). This compound was independently prepared by the following procedure. A solution of 1,2-dimethyl-5-nitroindole[2b] (0·35 g) in dimethylformamide (2 ml) was slowly added to a mixture of $POCl_3$ (0·3 ml) and dimethylformamide (0·75 ml), while cooling in a salt-ice bath. After the addition, stirring was continued 30 min at room temp, then 1 hr at 50°. Crushed ice (5 g) and 30% NaOH aq (4 ml) was then added; the mixture was heated to boiling,

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[5] Prepared by formylation (Note 4) of 5-nitroindole. The product (m.p. 300–302°), obtained in 60% yield, was identical with an authentic sample prepared by nitration of indole-3-aldehyde.[2a]

[6] J. J. Blanksma, *Rec. Trav. Chim.* 21, 275 (1902).

[7] J. S. Morley and J. C. E. Simpson, *J. Chem. Soc.* 360 (1948).

[8] Prepared in 95% yield by formylation of 1,2-dimethylindole. This product was identical with an authentic sample prepared by the method of Rodionov and Veselovskaya (Ref. 4).

allowed to cool, and filtered. The residue was washed with water, dried (0·38 g), and recrystallized from EtOH to give VIIa as yellow needles, m.p. 206–208°, λ_{max}^{EtOH} (log ε) 269 (4·45), 320 (3·97) mμ; IR 6·10(s), 6·66(s), 7·52(s), 7·70(s), 9·20(s), 9·61(m), 9·79(m), 10·86(m), 11·08(m), 11·25(s), 12·06(m), 12·60(s), 13·18(w), 13·42(m) μ. (Found: C, 60·95; H, 4·90; N, 12·83. $C_{11}H_{10}N_2O_3$ requires: C, 60·54; H, 4·62; N, 12·84%). IR and UV spectra of a mixture containing 57% of this compound and 43% of VIIb were identical with analogous spectra of the nitration mixture of VI.

1,2-*Dimethyl-6-nitroindole-3-aldehyde* (VIIb). Structure proof of VIIb obtained on nitration of VI was provided by the following synthesis. To a suspension of 2-methyl-6-nitroindole-3-aldehyde[1] (0·5 g) in 10% NaOH aq (15 ml) was added dropwise and with stirring 1·95 ml of dimethyl sulphate. After 2 hr, a second portion of dimethyl sulphate (0·2 ml) and 10% NaOH aq (10 ml) was added. Stirring was continued for 1 hr, then, after addition of a last portion (30 ml) of 10% NaOH aq, the mixture was heated gently on a water bath and filtered. The residue was washed with water, dried (0·33 g), and extracted with benzene, substantial amounts of tarry decomposition products remaining insoluble. Addition of pet. ether to the benzene extract caused precipitation of VIIb (0·09 g), which was purified by crystallization from benzene–pet. ether, and was identical with the previously obtained product.

Degradation of the mixture of VIIa *and* VIIb. A suspension of the crude nitration mixture (1·0 g) in glacial acetic acid (20 ml) and 30% H_2O_2 (3·5 ml) was allowed to stand 8 days at room temp, with occasional swirling. The resulting solution was then evaporated under red. press., and the residue (1·12 g) was fractionally crystallized from benzene–EtOH to give 0·55 g of a product (m.p. 150–160° dec), identified by its IR spectrum as a mixture of N-*acetyl*-N-*methyl-4-nitroanthranilic acid*[9] (VIIIb) and N-*acetyl*-N-*methyl-5-nitroanthranilic acid* (VIIIa). Identification of the latter compound was provided by the following synthesis. A suspension of 1,2-dimethyl-5-nitroindole[8b] (0·5 g) in glacial acetic acid (12 ml) and 30% H_2O_2 (2 ml) was heated 45 min on a water bath. The solvents were then removed under red. press., and the residue was crystallized twice from ethyl acetate to yield 0·22 g of VIIIa, m.p. 195–197° dec (the compound solidifies again above 200° to melt eventually at 270–272°). (Found: C, 50·47; H, 4·51. $C_{10}H_{10}N_2O_5$ requires: C, 50·42; H, 4·23%). All attempts to separate VIIIa and VIIIb by chromatography were unsuccessful.

The mixture of VIIIa and VIIIb (0·25 g) was dissolved in conc. H_2SO_4 (5 ml); the solution was heated 45 min on a water bath and poured onto crushed ice. The precipitate was filtered, thoroughly washed with water and dried (0·17 g; m.p. 225–243°) to yield a mixture of N-*methyl-5-nitro-* and N-*methyl-4-nitroanthranilic acid* (IIIa and IIIb). The IR spectrum of this mixture was essentially identical with the spectrum of the analogous mixture obtained on degradation of IIa and IIb.

Esterification of the acids IIIa and IIIb with MeOH–HCl and separation of the methyl esters IVa and IVb could be effected as described above, 0·11 g of the mixture of acids yielding 32 mg of IVb, m.p. 124–126°, and 50 mg of IVa, m.p. 144–145°.

Nitration of 2-*methylindole*-3-*aldehyde* (XI). One gram of this compound was nitrated as described for I. IR and UV analysis of the crude nitration product (1·18 g, 92%; m.p. 275–280° dec) showed its components to be 2-*methyl-5-nitroindole-3-aldehyde* (XIIa, 58%) and 2-*methyl-6-nitroindole-3-aldehyde*[1] (XIIb, 42%; λ_{max}^{EtOH} (log ε) 283 (4·36), 343 (3·98) mμ). Fractional crystallization of the nitration mixture from acetone allowed separation of a small amount of the less soluble XIIa as small, pale-yellow prisms, which did not melt when heated up to 320°[10]; λ_{max}^{EtOH} (log ε) 259 (4·43), 318 (4·00) mμ; IR 3·16(m), 6·12(s), 6·60(m), 6·80(s), 7·23(s), 7·48(s), 8·70(m), 11·13(m), 11·75(w), 12·20(w), 12·90(w), 13·19(w), 13·48(w), 14·08(w) μ. (Found: 59·01; H, 4·18; N, 13·78. $C_{10}H_8N_2O_3$ requires: C, 58·82; H, 3·95; N, 13·72%). All attempts to separate XIIa and XIIb by chromatography were unsuccessful.

Structure proof of 2-*methyl-5-nitroindole-3-aldehyde* (XIIa). A suspension of XIIa (0·13 g) in glacial acetic acid (5 ml) and 30% H_2O_2 (0·6 ml) was heated on a water bath until all the solid was dissolved (ca. 1 hr). The solution was then evaporated under red. press., and the solid residue was extracted with 10% Na_2CO_3. Acidification of the alkaline extract yielded 0·1 g of N-*acetyl-5-nitroanthranilic* acid[11] (XIIIa), m.p. 214–216°, identical with an authentic sample.

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[9] G. Berti and A. Da Settimo, *Gazz. Chim. Ital.* **90**, 525 (1960).

[10] The purity of this compound was demonstrated by the absence in its IR spectrum of the bands at 11·24, 12·00 and 14·30 μ, which belong to XIIb.

[11] H. Seidel and J. C. Bittner, *Monatsh.* **23**, 431 (1902).

Degradation of the mixture of XIIa *and* XIIb. A suspension of the crude nitration mixture (1·0 g) in glacial acetic acid (20 ml) and 30% H_2O_2 (4·2 ml) was allowed to stand 8 days at room temp, with occasional swirling. The resulting solution was evaporated under red. press. and the residue (1·1 g) was dissolved in ethyl acetate (charcoal). Fractional precipitation of this solution with pet. ether gave, after a few initial tarry fractions, 0·29 g of a solid, m.p. 177–187°, which consisted, on the basis of its IR spectrum, of a mixture of N-*acetyl-5-nitro-* (XIIIa) and N-*acetyl-4-nitroanthranilic acid*[11] (XIIIb). These acids could not be separated by chromatography over alumina.

Saponification of XIIIa and XIIIb was effected by heating 30 min on a water bath a solution of the mixture (0·2 g) in 2N NaOH aq (15 ml). Acidification of the alkaline solution yielded a mixture (0·11 g, m.p. 228–255°) of 4- and 5-*nitroanthranilic acid*[12] (XIVa and XIVb). This material was dissolved in abs. MeOH. Saturation of the solution with dry HCl, followed by distillation of the solvent gave a residue, which was thoroughly washed with 10% Na_2CO_3 aq, water, and dried to yield a mixture (60 mg; m.p. 112–125°) of *methyl 5-nitroanthranilate*[13] (XVa) and methyl 4-nitroanthranilate[14] (XVb). Separation of this mixture, effected by chromatography through a 0·9 × 35 cm column of neutral alumina, using benzene as eluant, yielded 20 mg of XVb, m.p. 156–157°. Further elution with ethyl ether yielded 22 mg of XVa, m.p. 162–164°. Both esters were identical with authentic samples.

Acknowledgment—We take pleasure in thanking Dr. Oreste Livi for carrying out part of the experimental work.

[12] M. Yanagita and M. Kubota, *J. Pharm. Soc. Japan* **72**, 845 (1952); *Chem. Abstr.* **47**, 3269 (1953).

[13] M. T. Bogert and G. Scatchard, *J. Amer. Chem. Soc.* **41**, 2066 (1919).

[14] H. L. Wheeler and B. Barnes, *J. Amer. Chem. Soc.* **20**, 221 (1898).