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SUBSTITUTED 2-METHYL- AND 2-METHYLENEINDOLINES.

2.* NITRO- AND AMINO-SUBSTITUTED 2-METHYL- AND 2-METHYLENE-INDOLINES

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From 5- and 6-aminotetramethylindolines, 2-methyleneindolines have been synthesized; these compounds can be condensed with other heterocyclic systems. The nitration of 1,2,3,3-tetramethylindoline under different conditions was studied.

In an earlier paper we described a method of synthesizing 2-methylenindolines from an industrially available Fischer base; substituents were introduced into the benzene ring of 1,2,3,3-tetramethylindoline I and the substituted compounds then oxidized [1]. The present work deals with the syntheses of 5- and 6-amino-1,2,3,3-tetramethylindolines – starting compounds for the preparation of the 2-methylenindolines, which can be condensed with other nitrogen-containing heterocyclics.

Nitration of the indoline I using a nitrating mixture generally used for the nitration of dimethylaniline [2] gave 6-nitroindoline II in good yield. The 4,6-dinitroindoline III and 6-nitro-2-methyleneindoline IV were also isolated from the reaction mixture. The indolines II-IV were easily separated because of their different basicities. Due to the effect of the substituents, nitration of the indoline I took place only at the meta-position relative to the dialkylamino group. Under the same conditions, nitration of dimethylaniline gives up to 30% of the para-isomer [2].

It is proposed that the indolines III and IV are the products of further reaction of compound II, and that the indoline IV is formed as a result of oxidation or nitration of the tertiary carbon atom [3]. We carried out a series of experiments on the formation of the mixture of III and IV from the indoline II. Nitration in a mixture of concentrated sulfuric and nitric acids gave a complex mixture of reaction products from which only the indoline IV was separated in 25% yield.

*For communication 1, see [1].

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TABLE 1. Spectral Data for Compounds II–IV and VI–XII

Compound	PMR spectra, δ, ppm: J, Hz										IR spectra, cm^{-1}
	N–CH_3 (1)	CH_3 (2)	2-H	CH_3 (3)	CH_3 (3)	4-H	5-H	6-H	7-H	remaining protons	
II	2,76	1,19	3,08 J=6,6	1,05	1,30	7,04	7,60 $J_{4,5}$=8; $J_{5,7}$=1,8	—	7,20	—	1603 (CH), 1525, 1350 (NO_2)
III	2,95	1,32	3,60 J=6,6	1,20	1,38	—	8,62	— $J_{5,7}$=2,2	7,86	—	1630, 1597 (CH); 1531, 1334 (NO_2)
IV*	3,10	3,97 (=CH_2)		1,36		7,13	7,64 $J_{4,5}$=8; $J_{5,7}$=2,2	—	7,28	—	1659 (=CH_2); 1603 (CH); 1523, 1350 (NO_2)
VII	3,16	4,35 / 4,49 (=CH_2) J_V=2,7		1,43		—	8,61	— $J_{5,7}$=2,3	7,98	—	1660 (=CH_2); 1630, 1597 (CH); 1530, 1334 (NO_2)
VI	3,30	—		1,44		8,11 $J_{4,5}$=1,8	—	8,27 $J_{6,7}$=8,5	6,93	—	1730 (C=O); 1610, 1490 (CH); 1510, 1330 (NO_2)
VIII	2,65	1,16	2,84 J=6,6	0,97	1,23	6,80	6,08 $J_{4,5}$=7,7;	— $J_{5,7}$=1,8	5,89	3,52 (NH)	3443, 3463 (NH_2); 1631, 1500 (CH)
IX	2,60	1,14	2,69 J=6,6	0,97	1,21	6,38...6,41				3,29 (NH_2)	3438, 3340 (NH_2)
X	2,93	1,16	3,45 J=6,6	1,09	1,26	7,20	—	7,35	6,50	—	—
XIb	2,67	1,17	2,83 J=6,6	1,00	1,26	7,18	— $J_{4,6}$=2,0;	7,11 $J_{6,7}$=7,5	6,44	2,12 ($CH_3C(O)$) 6,77 (NH)	1655 (C=O); 1613, 1564, 1494 (CH)
XIa	2,68	1,18	2,90 J=6,6	0,98	1,25	6,67	6,93 $J_{4,5}$=1,1;	— $J_{5,7}$=9	6,83	2,14 ($CH_3C(O)$) 7,27 (NH)	1660 (C=O); 1625, 1563, 1496 (CH)
XIIb	2,72	1,18	3,00	1,02	1,26	6,71	— $J_{4,6}$=2,2;	6,81 $J_{6,7}$=8	6,48	2,28 ($CH_3C(O)$)	1712 (C=O); 1607, 1493 (CH)
XII	2,68	1,18	2,99 J=6,6	1,03	1,29	7,01	6,44 $J_{4,5}$=7,8;	— $J_{5,7}$=2	6,18	2,31 ($CH_3C(O)$)	1710 (C=O); 1610, 1490 (CH)

*Data from [5].

EXPERIMENTAL

IR spectra of the compounds in KBr pellets or as thin films were taken on a UR-20 instrument, PMR on a Bruker WP-100 SY spectrometer using $CDCl_3$ as solvent and TMS as an internal standard. Elemental analysis data (C, H, N) agreed with the calculated values.

Nitration of 1,2,3,3-tetramethylindoline (I). To 300 ml of H_2SO_4 with mixing was added 2 moles of 1,2,3,3-tetramethylindoline at such a rate that the temperature did not exceed 25°C. The solution was cooled with chloroform and liquid nitrogen and the nitrating mixture, consisting of 132 ml (2.1 mole) of concentrated HNO_3 (d 1.42) and 120 ml of concentrated H_2SO_4, was added at a rate such that the temperature remained at between −8° and −17°C (1 h and 30 min). When the addition was complete, the mixture had become viscous. The reaction mixture was left in the cooling mixture for 2 h and 30 min, and the temperature then increased to 15°C. The reaction mixture was quickly poured into 3.5 liters of ice water, whereupon a dark oil separated which quickly hardened to give orange lumps. After a short time, a flocculent yellow-orange precipitate formed. The lumps were collected separately, crushed and refluxed with 200 ml of concentrated HCl, cooled and the insoluble precipitate filtered off. Recrystallization from a large quantity of heptane gave about 0.2 mole (10%) of dinitroindoline III ($C_{12}H_{15}N_3O_4$) with mp 102-103°C.

The flocculent precipitate was filtered off, and washed with aqueous ammonia. The filtrate was brought to pH 3 by the addition of aqueous ammonia at a temperature below 35°C, filtered again, and the precipitated material washed with water. The combined precipitates were dried, and recrystallized from heptane (freezing out) to give 1.4 mole (70%) of indoline II ($C_{12}H_{16}N_2O_2$) with mp 61-62°C. To the filtrate was added excess ammonia, the precipitate filtered off and recrystallized from heptane to give 0.14 mole (7%) of 2-methyleneindoline IV, mp 142-143°C (literature value [10], mp 143-144°C). IR and PMR spectral data were in agreement with the literature values [5, 10].

1,3,3-Trimethyl-2-methylene-6-nitroindoline (IV). A solution of 0.013 mole of the indoline II in a mixture of 10 ml of concentrated H_2SO_4 and 3 ml of water was cooled to −15°C, and a cooled (−15°C) mixture of 1.15 ml (0.014 mole) of 59% HNO_3 and 1.5 ml of concentrated H_2SO_4 added. The reaction mixture was kept at 20°C for 24 h, 30 g of ice added, and aqueous ammonia slowly added until the solution was alkaline. The precipitate was filtered off and purified by recrystallization from pentane. Yield 91%. Physical constants agreed with those of compound IV.

1,3,3-Trimethyl-2-methylene-4,6-dinitroindoline (VII, $C_{12}H_{13}N_3O_4$). This was obtained in the same way. The reaction mixture was kept at 20°C for 2 h, until the onset of gas evolution, when it was made alkaline. It was purified by fractional crystallization from octane and methanol. Yield 24%, mp 166-168°C.

1,3,3-Trimethyl-5-nitrooxoindole (VI, $C_{11}H_{12}N_2O_3$). To a solution of 9 mmole of V in 3 ml of trifluoroacetic acid was added a solution of 1.75 g (∿0.02 mole) of 57% of HNO_3 in 25 ml of acetic anhydride with cooling. After 5 minutes, the mixture began to heat up, and was then cooled and allowed to stand for 2 h. The reaction mixture was poured into aqueous ammonia at such a rate that the temperature did not rise above 30°C. The yellow powder was filtered off and after drying, was recrystallized from methanol to give 43%, of VI with mp 204-205°C.

1,2,3,3-Tetramethyl-6-aminoindoline (VIII, $C_{12}H_{18}N_2$). A. A mixture of 0.25 mole of indoline II in 500 methanol was heated in an autoclave with 3 g of Raney nickel for 2 h at 15 atm and 50°C. The methanol was evaporated off and the reaction product purified by distillation in vacuum. Yield 86%, mp 84-86°C (0.06 mm Hg).

B. Reduction with tin. To a solution of 0.19 mole of indoline II in 200 ml of concentrated HCl was added portionwise with mixing 0.67 mole of tin, such that the temperature of the reaction mixture did not rise above 50°C. The reaction mixture was then heated for 1 h and 30 min at 100°C until completely dissolved. When cool, the solution was neutralized with alkali, extracted with ether and purified by distillation. Yield 70%.

1,2,3,3-Tetramethyl-5-aminoindoline (IX, $C_{12}H_{18}N_2$). A. This was obtained from indoline V in the same way as the indoline VIIIA. The reaction mixture was kept for 3 h at 100 atm and 120°C. Evaporation of the methanol gave a dark brown powder, which was purified by vacuum distillation. Yield 77%, bp 93-95°C (0.05 mm Hg), mp 81-83°C.

B. To a solution of 0.23 mole of indoline I in 180 ml of 5 N HCl, cooled to −10°C, was added with mixing a cooled solution of 0.25 mole of sodium nitrate in 70 ml of water. The temperature of the reaction mixture was kept below −5°C. When all the sodium nitrite had been added, the reaction mixture was stirred for 1 h, and the temperature raised to 0°C. The product was neutralized and purified as in method A.

Nitrosation of the indoline I was carried out in the same way as nitrosation of dimethylaniline [11]. Compound X separated in the form of a brown oil and was recovered in methanol. Recovery was carried out analogously for indoline VIII (method A). Yield 72%.

1,2,3,3-Tetramethyl-5-acetylaminoindoline (XIa, $C_{14}H_{20}N_2O$). To a solution of 0.05 mole of aminoindoline IX in 15 ml of benzene and 6 ml of triethylamine at 5°C was added 0.05 mole of acetyl chloride in 10 ml of benzene, and the mixture kept at 20°C for 24 h. The triethylamine hydrochloride was filtered off, the benzene evaporated under vacuum and the residue triturated with hexane. An analytical sample was recrystallized from heptane. Yield 86%, mp 102-103°C.

1,2,3,3-Tetramethyl-6-acetylaminoindoline (XIb, $C_{14}H_{20}N_2O$). This was obtained and purified in the same way as the indole XI. Yield 78%, mp 95-96°C.

1,2,3,3-Tetramethyl-5-diacetylaminoindoline (XIIa, $C_{16}H_{22}N_2O_2$). A solution of 0.05 mole of aminoindoline IX in 35 ml of acetic anhydride was kept at 110°C for 2 h. The acetic anhydride was evaporated off under vacuum, the residue dissolved in 35 ml of chloroform and the solution washed with aqueous ammonia. After drying and evaporation of the chloroform, the product was triturated with heptane and recrystallized from heptane. Yield 72%, mp 92-93°C.

1,2,3,3-Tetramethyl-6-diacetylaminoindoline (XIIb, $C_{16}H_{22}N_2O_2$). This was obtained and purified in the same way as the preceding compound. Yield 69%, mp 93-94°C.

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