Preparation and Spectra of Some Acetyl Derivatives of 2,4-Toluenediamine

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The preparation and spectral properties of several acetyl derivatives of 2,4-toluenediamine, 2-acetylamino-4-aminotoluene, 4-acetylamino-2-aminotoluene, 2,4-diacetylaminotoluene, and 2-amino-4-diacetylaminotoluene are described.

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2,4-Toluenediamine, an intermediate in polyurethane foam and elastomer production, has a carcinogenic effect in rats (*2, 3, 6*). Acetylaminotoluenes are possible metabolites of 2,4-toluenediamine, and the purpose of this study was to prepare various acetylated derivatives of 2,4-toluenediamine for determining spectral and other physicochemical characteristics. This information is being used to identify 2,4-toluenediamine metabolites as well as to help define the effects of chemical structure on the acute and chronic toxicity in animals.

Table I. Physical Data, Yields, and Synthetic Conditions

Final compound	Starting material	Conditions	Solvent of crystallization and form	Mp, °C	Yield, %
2-Amino-4-nitrotoluene (I)	A. o-Toluidine	5 ml o-toluidine 60 ml conc H_2SO_4 (96.4%) 5 ml conc HNO_3 (70–71%) Ice bath temp	50% Ethanol Yellow crystals	105–106	84
	B. 2,4-Dinitrotoluene	1.8 g 2,4-dinitrotoluene 20 ml ethanol 15 ml $(NH_4)_2S$ soln 50° for 15 min Column chromatography on silica gel G ($CHCl_3$-CH_3OH)	$CHCl_3$ Yellow crystals	104–105	33
2-Acetylamino-4-nitrotoluene (II)	2-Amino-4-nitrotoluene	5 g I 8 ml Ac_2O 5 ml AcOH 50° for 10 min	50% Ethanol Yellow needles	149–150	71
2-Acetylamino-4-aminotoluene (III)	II	3.5 g II, 3.5 g Fe powder 8.5 ml AcOH 50 ml H_2O 18 ml ethanol, reflux 30 min; evaporate; neutralize (Na_2CO_3); evaporate filtrate	60% Ethanol Pale yellow needles	138–139	63
4-Acetylamino-2-aminotoluene	2,4-Toluenediamine	3 g 2,4-toluenediamine 2.4 ml AcOH 0.6 ml H_2O React 85° for 30 min	Water White needles	158–159	22
2,4-Diacetylaminotoluene	2,4-Toluenediamine	3 g 2,4-toluenediamine 5.2 ml Ac_2O 415 ml benzene Reflux 10 min	Water (Norit) Fluffy white needles	221–222	90
4-Diacetylamino-2-nitrotoluene	4-Methyl-3-nitroaniline	5 g 4-methyl-3-nitroaniline 100 ml Ac_2O; reflux 4 hr; pour into H_2O	Ethanol	77–78	78
4-Diacetylamino-2-aminotoluene[b]	4-Diacetylamino-2-nitrotoluene	1 g 4-diacetylamino-2-nitrotoluene; 0.93 g cyclohexene; 25 mg Pd black in 11.34 ml ethanol; reflux 17 hr; isolate by tlc ($CHCl_3$:benzene:ethyl acetate 70:15:15:3 [v/v]) (develop only once-repeated development leads to rearrangement)			Approx 87

[a] Elemental analyses (C,H,N) in agreement with theoretical values were obtained and submitted for review. [b] No elemental analysis because of decomposition on attempts to recrystallize.

Table II. Infrared and Ultraviolet Spectra for 2,4-Toluenediamine Derivatives

Compound	Major infrared[a] absorptions, cm^{-1}	Ultraviolet[b] spectra	$\mu g/ml$, nm[c]
2-Acetylamino-4-aminotoluene	3400, 3270 (N—H) 2915 (C—H), 1650 (C=O) 1575, 1525 (C—N) 1300, 1260 (N—H) 875, 812, 790 (=CH)[e]	213 (21,100) 235 (11,900) (s)[d] 297 (2,610)	9.8 (213)
4-Acetylamino-2-aminotoluene	3410, 3320 (N—H) 2905 (C—H), 1650 (C=O) 1545, 1510 (C—N) 1330, 1264 (N—H) 858, 790 (—CH)[e]	222 (29,200) 243 (12,000) (s)[d] 297 (3,680)	5.7 (222)
2,4-Diacetylamino-toluene	3300 (N—H), 2920 (C—H) 1650 (C=O), 1550 1525 (C—N), 1320 1280, 1260 (N—H) 895, 819, 809 (=CH)[e]	240 (19,100) 215 (18,600) 285 (1,810) (s)[d]	10.4 (240)
4-Diacetylamino-2-nitrotoluene	2950 (C—H), 1680 (C—N) 1650 (C=O), 1540 884, 868, 815 (=CH)	215 (18,000) 262 (3,900) 285 (850)	13.09 (215)
4-Diacetylamino-2-aminotoluene		232[f] 237 302	1.77 (232)

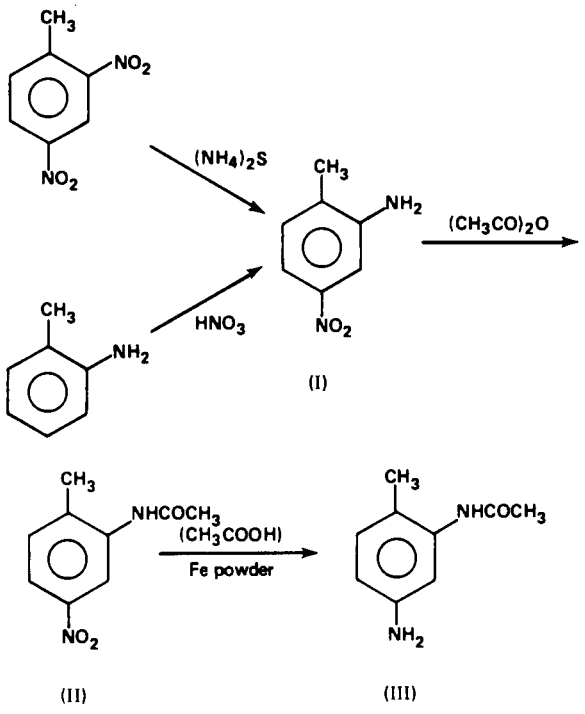
[a] All infrared samples were taken as a Nujol mull. [b] Figures in parentheses are ϵ values of peaks. Absolute methanol used as solvent, scanning between 340–190 nm. [c] The concentration which gives absorbance 1. [d] Median wavelength of a shoulder. (s) = shoulder. [e] 1,2,4-Trisubstituted benzene ring. [f] ϵ values not calculated because of difficulty in determining actual weight of sample.

Table III. Nuclear Magnetic Resonance and Mass Spectra of 2,4-Toluenediamine Derivatives

Compound	δ, ppm[a]	J, Hz	No. of protons	Assignment	Spectra, m/e[b]
2-Acetylamino-4-aminotoluene	2.00 s[c]		6H	$-CH_3$, $-CO-CH_3$	164 (95), 122 (70), 121 (100), 105 (17), 95 (14), 94 (7), 77 (12), 51 (6), 43 (17)
	4.75 s		2H	$-NH_2$	
				Aromatic protons	
	6.73 d	$J_{56} = 8.5$	1H	6-H	
	6.64 d	$J_{35} = 2.5$	1H	3-H	
	6.25 q		1H	5-H	
	8.90 s		2H	—NH—CO—	
4-Acetylamino-2-aminotoluene	2.00 s		6H	$-CH_3$, $-CO-CH_3$	164 (87), 122 (100), 121 (83), 105 (18), 95 (5), 94 (15), 77 (13), 51 (5), 43 (16)
	4.67 s		2H	$-NH_2$	
				Aromatic protons	
	6.73 d	$J_{56} = 8.0$	1H	6-H	
	6.89 d	$J_{35} = 2.0$	1H	3-H	
	6.58 q		1H	5-H	
	9.47 s		1H	—NH—CO—	
2,4-Diacetylamino-toluene	2.00 s		3H	$-CH_3$,2-CO—CH_3	206 (46), 164 (52), 122 (100), 121 (79), 105 (10), 94 (12), 77 (11), 43 (33)
	2.03 s		3H		
	2.12 s		3H		
	7.04 d	$J_{56} = 8.5$	1H	6-H	
	7.60 d	$J_{35} = 2.0$	1H	3-H	
	7.30 2 d		1H	5-H	
	9.16 s		1H	—NH—CO—	
	9.76 s		1H	—NH—CO—	
4-Diacetylamino-2-nitrotoluene	2.20 s		6H	2-CO—CH_3	236 (10), 194 (89), 177 (34), 152 (17), 135 (45), 107 (44), 43 (100)
	2.55 s		3H	$-CH_3$	
	7.98 d	$J_{35} = 2$	1H	3-H	
	7.50 bs		2H	5-H, 6-H	
4-Diacetylamino-2-aminotoluene	2.13		3H	$-CH_3$	206 (15), 164 (76), 122 (100), 121 (60), 43 (29)
	2.16		6H	2-CO—CH_3	
	4.99		2H	$-NH_2$	
	7.01 d	$J_{56} = 7.9$	1H	6-H	
	6.45 d	$J_{35} = 2$	1H	3-H	
	6.34 q		1H	5-H	

[a] Samples were run at 60 MHz in DMSO-d_6 except for 4-diacetylamino-2-aminotoluene which was run at 100 MHz. [b] Figures in parentheses are relative intensities of peaks. All spectra were recorded at 70 eV ionizing voltage. [c] s, singlet; d, doublet; q, quartet; bs, broad singlet.

2-Acetylamino-4-aminotoluene was prepared according to the reaction scheme illustrated below:



(II) (III)

Compound I was prepared from *o*-toluidine by nitration according to Noelting and Collin (*5*). A better yield was obtained if the nitration mixture was neutralized with solid sodium carbonate. The Limpricht method (*4*), namely monoreduction of 2,4-dinitrotoluene with alcoholic ammonium sulfide, led to a mixture of I and the isomeric 4-amino-2-nitrotoluene. This could be separated by column chromatography on silica gel G with chloroform–methanol. Preliminary in vitro studies on the metabolism of 2,4-toluenediamine by liver fractions from various species indicated that a compound with a mass spectrum corresponding to a diacetylamino-amino toluene was a possible metabolite. Therefore, 4-methyl-3-nitroaniline was diacetylated and carefully reduced to 4-diacetylamino-2-aminotoluene. This compound rearranged readily to 2,4-diacetylaminotoluene if the usual reduction schemes were employed. Transfer-hydrogenation, with cyclohexene as hydrogen donor, was a feasible method (*1*). The essential conditions for preparation of the desired compounds, their physical constants, and analyses are given in Table I.

The various spectra of the acetylaminotoluenes are given in Tables II and III. Even though the maxima of 2-acetylamino-4-aminotoluene and 4-acetylamino-2-aminotoluene are fairly close, the ultraviolet spectra are useful for identification. For positive determination of metabolites of 2,4-toluenediamine, we have found that a combination of spectral determinations, tlc, and gas chromatography–mass spectrometry is most useful.

Experimental

2,4-Toluenediamine (Aldrich Chemical Co., Inc.) had a maximum purity of 85% and mp 96–97°C. This commercial material, after purification by column chromatography on silica gel G (100–200 mesh) and PF_{254} with chloroform–methanol, had a minimum purity of 98.5% and mp 98–99°C. 4-Methyl-3-nitroaniline, mp 88–90°, was also from Aldrich. 2,4-Dinitrotoluene, purchased from Eastman Kodak Co., was 98% pure and had a mp of 70–72°C.

Melting points are uncorrected and were taken on a Kofler micro hot stage. Silica gel PF_{254} sheet (0.1-mm thickness) was used for tlc, and the spots were visualized with uv light. The infrared spectra were obtained with a Perkin-Elmer (127) infracord spectrophotometer. The nuclear magnetic resonance spectra (nmr) were taken on a Varian T60 spectrometer, and the mass spectra with a JMS-01SG-2 mass spectrometer. The ultraviolet spectra were obtained with a Beckman spectrophotometer, Acta III. Elemental analyses (C, H, N) were performed by the NIH microanalysis section, Bethesda, Md.

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