Aroylmethylamine Synthesis by Stephen Reduction of Aroyl Cyanides

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The Stephen reduction of nitriles normally gives rise to an aldimine complex that affords the aldehyde on hydrolysis.[1] Wibaut and Overhoff isolated 2,6-dichloro-4-aminomethylpyridine as the end product of the Stephen reduction of 2,6-dichloro-4-cyanopyridine.[2]

In the course of the synthesis of sympathomimetic amines, we observed that the reduction of aroyl cyanides by the Stephen method leads to the corresponding aroylmethylamine hydrochlorides in good yields. Table I summarizes the results.

TABLE I

STEPHEN REDUCTION OF AROYL CYANIDES

ArCOCN Ar⁻	$ArCOCH_2NH_3^+\ Cl^-$ Yield, %	Mp, °C
Phenyl[a]	67	184–186 dec[b]
2-Methylphenyl[c]	78	160–161 dec[b]
3-Methylphenyl[c]	50	174–175 dec[d]
4-Methylphenyl[c]	62	208–210 dec[d]
4-Methoxyphenyl[e]	60	197–199 dec[f]
3,4,5-Trimethoxyphenyl[g]	56	254–255 dec[h]
2-Furyl[i]	50	249–250 dec[j]

[a] T. S. Oakwood and C. A. Weisgerber, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1958, p 112. [b] S. Cheng, S. Jonsson, and F. T. Semeniuk, *J. Pharm. Sci.*, **51**, 108 (1962). [c] F. Asinger, A. Saus, H. Offermanns, and H. D. Hahn, *Justus Liebigs Ann. Chem.*, **691**, 92 (1966). [d] G. Jones, *J. Chem. Soc.*, 1918 (1960). [e] J. F. Eastman and S. Selman, *J. Org. Chem.*, **26**, 293 (1961). [f] H. E. Baumgarten and J. M. Petersen, *J. Amer. Chem. Soc.*, **82**, 459 (1960). [g] G. P. Schiemenz and H. Engelhard, *Chem. Ber.*, **92**, 1336 (1959). [h] A. Sonn, *ibid.*, **58**, 1103 (1925). [i] E. Fischer and F. Brauns, *ibid.*, **46**, 892 (1913). [j] O. Dann, H. Ulrich, and E. E. Moeller, *Z. Naturforsch.*, **7b**, 344 (1952).

The amino ketones can be reduced to amino alcohols with hydrogen in the presence of a palladium-on-carbon catalyst;[3] however, direct reduction of acyl cyanides to amino alcohols is perferred.[4]

Experimental Section

Reduction Procedure.—Anhydrous stannous chloride (28.0 g, 0.15 mol) in 100 ml of anhydrous ether was saturated with hydrogen chloride at room temperature. While the mixture was stirred in an ice–water bath, 0.1 mol of the aroyl cyanide was added dropwise. After 3 hr the mixture was filtered and the residue was washed with anhydrous ether. The residue was suspended in 500 ml of water containing 5 ml of hydrochloric acid, and was then saturated with H_2S. The tin sulfides were removed by filtration and the filtrate was evaporated in a rotary still. The residual aroymethylamine hydrochloride was purified by crystallization from acetone–ether.

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(1) E. Mossetig, *Org. React.*, **8**, 246 (1954).

(2) J. P. Wibaut and J. Overhoff, *Recl. Trav. Chim. Pays-Bas*, **52**, 55 (1933).

(3) G. N. Walker and M. A. Moore, *J. Org. Chem.*, **26**, 432 (1961).

(4) A. Burger and E. D. Hombaker, *J. Amer. Chem. Soc.*, **74**, 5514 (1952).

The Action of Hydrazine and Its Derivatives on the Addition Products of Allyl Isothiocyanate and Dimethyl Malonate. A Correction

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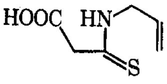
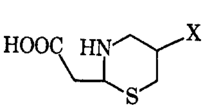
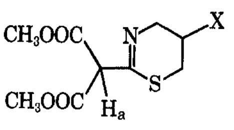
In connection with some other work, we needed samples of I and II, the preparation of which has been described by Worrell.[1]



I



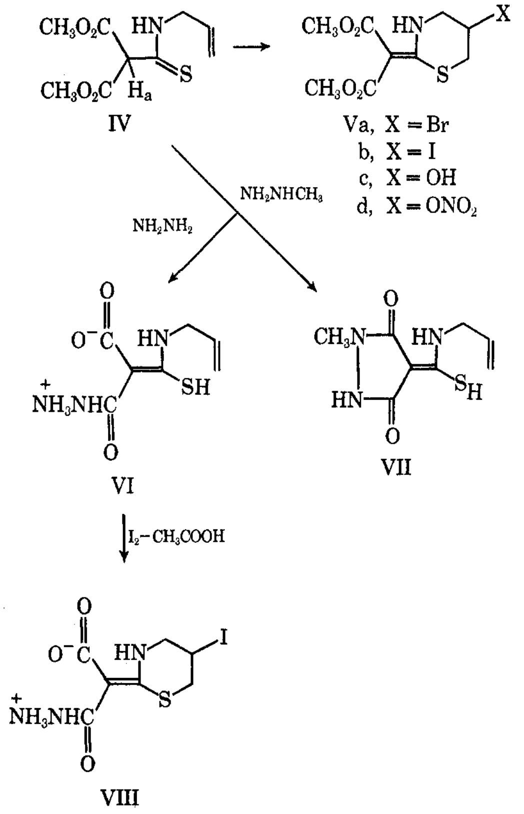
IIa, X = Cl
b, X = Br
c, X = I



III

Condensation of dimethyl malonate and allyl isothiocyanate gave IV. Hydrazinolysis of IV, followed by reaction with hydrochloric acid, did not, however, yield I, mp 120–121°, as described, but the hydrazide VI, mp 120–121° (Scheme I). No attempt was made to differentiate between the two possible geometric isomers.

SCHEME I



The structure of I had been based on its sufur analysis (Calcd for $C_6H_9O_2NS \cdot 2H_2O$: S, 16.4. Found:

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(1) D. E. Worrell, *J. Amer. Chem. Soc.*, **54**, 2061 (1932).

S, 16.4), which is close to that of VI (S, 15.95). Microanalysis indicated formula $C_7H_{11}O_2N_3S$ rather than $C_6H_{13}O_4NS$. The nmr spectrum of VI showed bands characteristic of the allyl group, which were in the same position as in the starting material IV, one low-field exchangeable proton at 10.1 ppm, and a broad band (5 H), the position of which was concentration dependent ($NH-N^+H_3$, NH, and SH). The major feature of the infrared spectrum was a very broad band at 3500–2300 cm^{-1}, typical of an amine salt.

Reaction of VI with iodine gave, as described, a compound, mp 213–214°, which does not have the structure of IIc, but VIII.[2]

In order to confirm the structure of the hydrazinolysis product VI, diester IV was treated in an analogous manner with methylhydrazine. The unstable product obtained appeared to have the cyclic structure VII,[2] as evidenced by its elemental analysis and nmr spectrum, which indicated the presence of an *N*-methyl group (δ 3.2 ppm, singlet), an allyl group, and only three exchangeable protons (D_2O).

Worrell's conversion of IV to Va and Vb could be duplicated. However, treatment of Va with alcoholic silver nitrate did not give the alcohol Vc as described,[1] but nitrate Vd. Compound Vd gave a positive test for the nitrate group (diphenylamine and sulfuric acid).[3]

It appears that the position of the double bond in Va and Vb is exocyclic and not endocyclic (III), as had been described. The assignment for the position of the double bond is based mainly on the nmr spectra of Va and Vb, which do not show the low-field proton H_a of compound IV (δ 5.6 ppm, singlet), but indicate the presence of a typical N-H proton at 3.0–6.0 ppm (broad band). In addition, Va and Vb absorb at longer wavelength [λ_{max}^{EtOH} 285 nm (ϵ 12,500)] than IV [λ_{max}^{EtOH} 274 nm (ϵ 13,400)].

The position of the double bond in VI and VII is based on the fact that both compounds form a cuprous salt (thiol),[4] and both show secondary amine absorption in their ir spectra. No experimental work was done to find out why reaction of IV with hydrazine and methylhydrazine gave the hydrazido acid VI and the pyrazolidinedione VII, respectively.

Experimental Section

Melting points were determined on a Gallenkamp block and are uncorrected. Mass spectra were obtained on an AE1-MS-902 mass spectrometer at 70 eV using a direct-insertion probe. Nmr spectra were recorded on a Varian Associates T-60 spectrometer. Ir spectra were obtained on a Unicam SP1000 and a Perkin-Elmer 257 infrared spectrophotometer. Ultraviolet spectra were determined with a Unicam SP-800 spectrophotometer. Microanalyses were carried out by A. Bernhardt Mikroanalytisches Laboratorium, Elbach uber Engelskirchen, and C. Daessle, Montreal.

Carbomethoxy Methyl Malonate Monothioallylamide (IV).—This compound was prepared according to the procedure of Worrell[1] with the following modification: the mixture of the sodium salt of dimethyl malonate and allyl isothiocyanate was refluxed for 24 hr with vigorous stirring. This ensured that most of the sodium metal had reacted and minimized the possibility of any large excess of sodium igniting when the mixture was poured into ice water. After recrystallization from ethyl alcohol–water, a 56% yield of IV was obtained: mp 42–43° (lit.[1] yield 66%; mp 42–43°); ir (KBr) 3335, 3385 (NH), 1750, 1715 cm^{-1} (C=O); nmr ($CDCl_3$) δ 3.9 (s, 6), 4.4 (t, 2), 5.6 (s, 1), 5.2–6.4 (m, 3), 4.0–6.0 (s, broad, NH); uv max (95% C_2H_5OH) 274 nm (ϵ 13,400); mass spectrum (70 eV) *m/e* 231 (M^+).

Anal. Calcd for $C_9H_{13}O_4NS$: C, 46.75; H, 5.62; N, 6.06; S, 13.85. Found: C, 47.03; H, 5.48; N, 5.87; S, 14.03.

Reaction of IV with Bromine (Va).—The procedure of Worrell was followed exactly: yield 68%; mp 152–154° (lit.[1] yield 68%; mp 153–154°); ir (KBr) 3200, 1615, 1650 cm^{-1}; nmr (DMSO-d_6) δ 3.9 (s, 6), 4.1 (m, 2), 3.6 (m, 3), 3.0–6.0 (broad, 1, NH); uv max (95% ethanol) 285 nm (ϵ 12,500); mass spectrum (70 eV) *m/e* 309 (M^+), 311 ($M^+ + 2$).

Anal. Calcd for $C_9H_{12}O_4NSBr$: C, 34.95; H, 3.88; N, 4.53; S, 10.36; Br, 25.85. Found: C, 34.92; H, 3.83; N, 4.53; S, 10.61; Br, 25.96.

The iodo derivative Vb was prepared in a similar manner, mp 156–157° (lit.[1] mp 156–157°).

Reaction of Va with Silver Nitrate (Vd).—This compound was prepared according to Worrell: yield 65%; mp 104–105° (lit.[1] mp 104–105°) (after drying under vacuum at 40°, mp 81–82°); ir (KBr) 3220, 1650, 1660, 1630 (ONO_2), 1285, 870–855 cm^{-1} (ON); nmr (DMSO-d_6) δ 3.8 (s, 6), 3.95 (m, 3), 4.7 (m, 2), 9.8 (broad, 1, NH); mass spectrum (70 eV) *m/e* 292 (M^+), 229 ($M^+ - HNO_3$). It was difficult to obtain good analytical values because of the unstability of Vd.

Anal. Calcd for $C_9H_{12}O_7N_2S$: C, 36.99; H, 4.11; N, 9.59; S, 10.95. Found: C, 37.48; H, 4.29; N, 9.63; S, 10.87.

Reaction of IV with Hydrazine (VI).—The procedure of Worrell was followed except for the following modification in the work-up: the concentrated deep red solution was added slowly, with vigorous stirring, to an iced solution of 5 *N* hydrochloric acid. If this was not strictly followed an intractable gum was obtained which could not be crystallized. During the reaction a strong odor of hydrogen sulfide was detected, probably due to gross decomposition of the thioamide. A 20% yield of crystalline product was obtained. It turned yellow upon standing for several weeks. Water of hydration was removed by drying the compound under vacuum at 60° for 4–6 days: mp 120–121°; ir (KBr) 3300, 3000–2300 (NH_3^+ str), 1630–1520 (C–O str), 1480, 1430, 1230, 1040, 1000, 940, 775 cm^{-1}; nmr (DMSO-d_6) δ 4.3 (t, 2), 5.35 (m, 1), 5.1 (m, 1), 6.0 (m, 1), 3.0–6.0 (broad, 5), 10.1 (broad, 1); uv max (95% C_2H_5OH) 293 nm (ϵ 16,500), 255 (14,300).

Anal. Calcd for $C_7H_{11}O_3N_3S$: C, 41.79; H, 5.47; N, 20.89; S, 15.95. Found: C, 42.02; H, 5.27; N, 21.16; S, 15.72.

Reaction of IV with Methylhydrazine (VII).—VII was prepared according to the procedure described for VI, except that the deep red solution was worked up after 2–3 hours. The resulting crystalline solid (25%) was recrystallized from ether–hexane: mp 186–188° (dried under vacuum at 40° overnight); ir (KBr) 3320, 2800–2700 (NCH_3); nmr (DMSO-d_6) δ 3.2 (s, 3), 4.5 (t, 2), 5.3 (m, 1), 5.6 (m, 1), 5.9 (m, 1), 4.0–9.0 (broad, 3, exchangeable with D_2O); uv max (95% EtOH) 295 nm (ϵ 18,800), 258 (16,000).

Anal. Calcd for $C_8H_{11}O_2N_3S$: C, 45.07; H, 5.16; N, 19.72; S, 15.02. Found: C, 45.53, 44.51; H, 5.13, 5.31; N, 19.96; S, 14.83.

Reaction of VI with Iodine (VIII).—The compound was prepared according to the published procedure.[1] The product was dried overnight under vacuum at 100° to yield 75% of a colorless, crystalline product: mp 213–214° (lit.[1] 213–214°); ir (KBr) 3300, 3000–2500 (NH_3^+), 1640 cm^{-1}; nmr (DMSO-d_6) δ 3.0 (m, 2), 3.3 (m, 2) 3.6 (m, 1), 5.0–10.0 (broad, 5, exchangeable with D_2O); uv max (95% EtOH) 295 nm (ϵ 22,400).

Anal. Calcd for $C_7H_{10}O_3N_3SI$: C, 24.50; H, 2.94; N, 12.25; S, 9.33; I, 37.01. Found: C, 24.67; H, 2.97; N, 12.43; S, 9.60; I, 37.11.

Registry No.—IV, 32444-37-4; Va, 32444-38-5; Vb, 32444-39-6; Vd, 32444-40-9; VI, 32444-41-0; VII, 32444-42-1; VIII, 32444-43-2; hydrazine, 302-01-2.

Acknowledgments.—We wish to thank the National Research Council of Canada for financial support.

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(2) See Experimental Section.

(3) F. Feigl, "Spot Tests in Organic Analysis," 7th ed, Elsevier, New York, N. Y., 1966, p 178.

(4) Reference 3, p 222.