Cyclization of Ethyl Acetoacetate and Substituted Salicylaldehydes in the Presence of Ammonium Acetate

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3-Methoxy- and 3,5-dibromo-salicylaldehydes condense with ethyl acetoacetate in the presence of ammonium acetate to give in each case a 1,2,5,6-tetrahydropyridine as the main product, together with a [1]benzopyrano-[3,4-*c*]pyridin-5-one.

We have previously shown that the condensation of active methylene compounds such as benzoylacetonitrile [1] and ethyl cyanoacetate [1,2] with salicylaldehyde or substituted salicylaldehydes gives heterocyclic products. We view these reactions as Knoevenagel condensations. However, the reaction of ethyl acetoacetate with substituted salicylaldehydes was found to produce compounds containing two salicylaldehyde residues. We now describe the cyclization reaction of ethyl acetoacetate with 3-methoxy- and 3,5-dibromo-salicylaldehyde in the presence of ammonium acetate.

In each case, reaction in refluxing ethanol gave a mixture of a tetrahydropyridine (1) (50—53%) and a [1]benzopyrano[3,4-*c*]pyridine (2) (7—10%), the former

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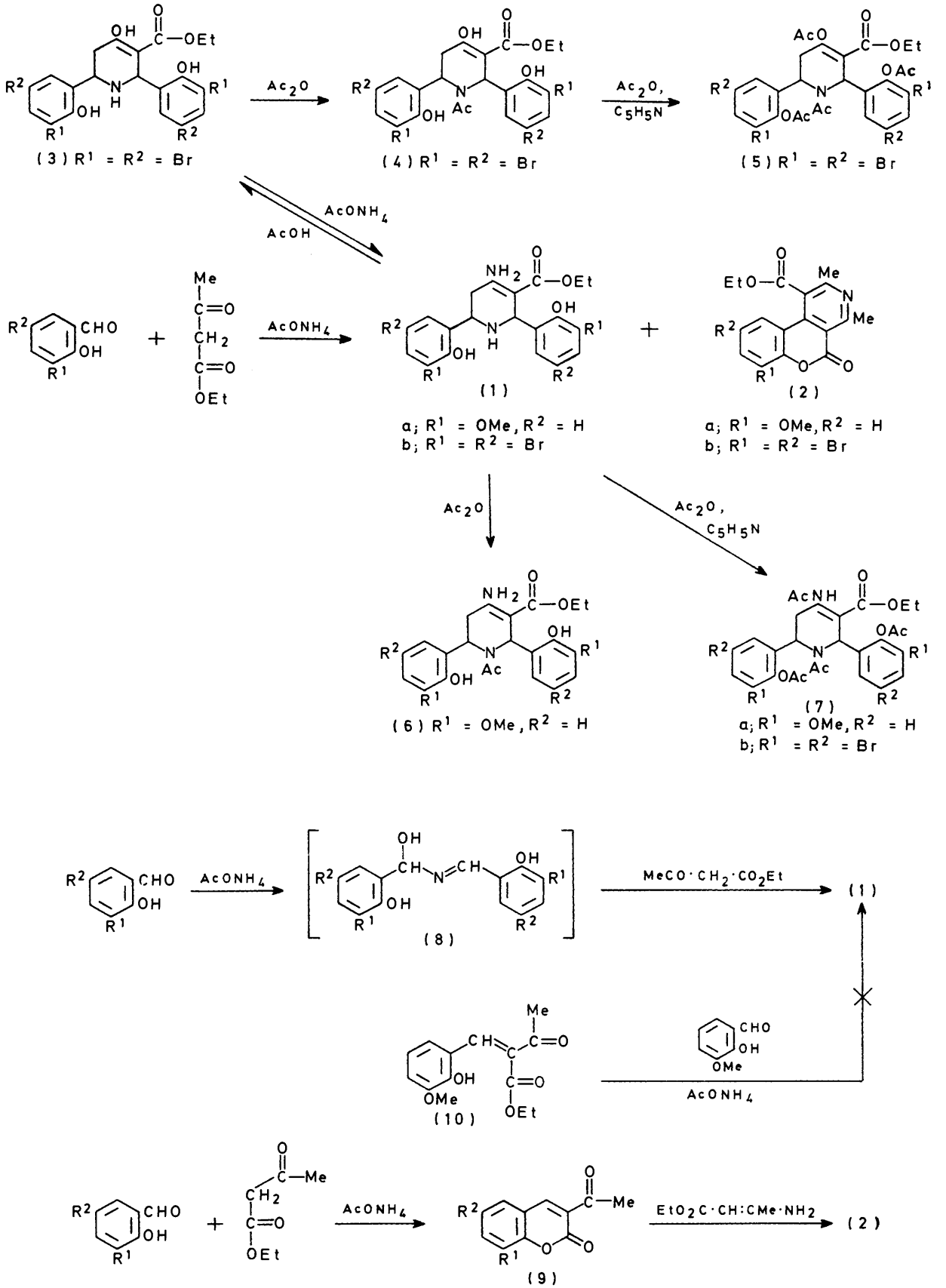
[2] A. Sakurai, H. Midorikawa, and Y. Hashimoto, *Bull. Chem. Soc. Japan*, 1970, **43**, 2925.


(3) R1 = R2 = Br
Ac2O
(4) R1 = R2 = Br
Ac2O, C5H5N
(5) R1 = R2 = Br
AcONH4
AcOH
AcONH4
(1)
(2)
a; R1 = OMe, R2 = H
b; R1 = R2 = Br
Ac2O
Ac2O, C5H5N
(6) R1 = OMe, R2 = H
(7)
a; R1 = OMe, R2 = H
b; R1 = R2 = Br
AcONH4
(8)
MeCO·CH2·CO2Et
(10)
AcONH4
AcONH4
(9)
EtO2C·CH:CMe·NH2

formed from ethyl acetoacetate, aldehyde, and ammonia in the ratio 1:2:2 and the latter from the reagents in the ratio 2:1:1. Both products were identified on the basis of spectral data (see Experimental section). The structure (1) was confirmed by the following reactions. Treatment of compound (1b) with acetic acid in ethanol gave the 4-hydroxy-derivative (3), which was reconverted into (1b) by refluxing with ammonium acetate in ethanol. The reaction of compound (3) with acetic anhydride afforded the *N*-acetyl derivative (4), which gave the tetra-acetyl derivative (5) on further treatment with acetic anhydride in boiling pyridine. Treatment of compound (1a) with acetic anhydride afforded the mono-*N*-acetyl derivative (6) or the tetra-acetyl derivative (7a), depending on the conditions.

The mode of formation of compound (1) can be envisaged as follows. Two molecules of aldehyde condense with one of ammonia to yield the hydroxy-imine (8), which reacts with ethyl acetoacetate and another molecule of ammonia to form (1). In support of this, treatment of 3-methoxysalicylaldehyde with the product (10) of a Knoevenagel condensation of ethyl acetoacetate and 3-methoxysalicylaldehyde, in the presence of ammonium acetate, did not give the heterocycle (1). Compound (2) could be formed by condensation of the aldehyde first with ethyl acetoacetate to give the benzopyranone (9), which then reacts with ethyl β-aminocrotonate (from ethyl acetoacetate and ammonia).

EXPERIMENTAL

I.r. spectra (KBr discs) were determined with a Perkin-Elmer 521 grating spectrophotometer, and n.m.r. spectra with a Varian HA 100 spectrometer (tetramethylsilane as internal reference).

Reaction of Ethyl Acetoacetate with 3-Methoxysalicylaldehyde and Ammonium Acetate.—Ammonium acetate (3.08 g, 0.04 mol) was added to a solution of ethyl acetoacetate (3.90 g, 0.03 mol) and 3-methoxysalicylaldehyde (4.56 g, 0.03 mol) in ethanol (30 ml), and the mixture was heated under reflux for 0.5 h. Pale yellow crystals precipitated during the reaction were collected and washed with hot methanol. Recrystallization from pyridine–methanol gave *ethyl 4-amino-1,2,5,6-tetrahydro-2,6-bis-(2-hydroxy-3-methoxyphenyl)-pyridine-3-carboxylate* (1a) (3.1 g, 50%), m.p. 198—200° (decomp.), $\nu_{max.}$ 3 450, 3 340 (NH_2), 3 410 (OH), 3 280 (NH), and 1 660 cm^{-1} (C=O), δ (C_5D_5N) 0.98 (3 H, t, CH_3, *J* 3.5 Hz), 3.0 (2 H, d, ring CH_2, *J* 4.0 Hz), 3.64 (6 H, s, 2 OCH_3), 4.12 (2 H, q, ester CH_2, *J* 3.5 Hz), 4.60 (1H, t, ring CH, *J* 4.0 Hz), 6.06 (1 H, s, ring CH), 6.70—7.20 (6 H, m, aromatic), and 7.60—8.30br (2 H, NH_2) (Found: C, 63.7; H, 6.25; N, 6.8. $C_{22}H_{26}N_2O_6$ requires C, 63.8; H, 6.3; N, 6.8%).

The filtrate was left at room temperature for several days.

The resulting solid was filtered off and recrystallized from ethanol giving *ethyl 2,4-dimethyl-7-methoxy-5-oxo[1]benzopyrano[3,4-c]pyridine-1-carboxylate* (2a) (0.7 g, 7%), m.p. 146—148°, δ ($CDCl_3$) 1.44 (3 H, t, ester CH_3, *J* 3.5 Hz), 2.66 and 2.80 (3 H, s, CH_3), 4.0 (3 H, s, OCH_3), 4.50 (2 H, q, ester CH_2, *J* 3.5 Hz), and 7.0—8.14 (3 H, m, aromatic) (Found: C, 66.1; H, 5.3; N, 4.1. $C_{18}H_{17}NO_5$ requires C, 66.05; H, 5.2; N, 4.3%).

Reaction of Ethyl Acetoacetate with 3,5-Dibromosalicylaldehyde and Ammonium Acetate.—To a mixture of ethyl acetoacetate (3.9 g, 0.03 mol) and 3,5-dibromosalicylaldehyde (8.4 g, 0.03 mol) in ethanol (35 ml), ammonium acetate (3.08 g, 0.04 mol) was added, and the mixture was heated for 0.5 h. The pale yellow solid deposited was collected and recrystallized from pyridine–methanol to give *ethyl 4-amino-2,6-bis-(3,5-dibromo-2-hydroxyphenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate* (1b) (5.4 g, 53%), m.p. 196—197° (decomp.), $\nu_{max.}$ 3 450, 3 340 (NH_2), 3 390 (OH), 3 250 (NH), and 1 675 cm^{-1} (C=O) (Found: C, 35.8; H, 2.8; Br, 47.8; N, 4.1. $C_{20}H_{18}Br_4N_2O_4$ requires C, 35.8; H, 2.7; Br, 47.8; N, 4.2%)

The filtrate was kept at room temperature for several days, then the yellow crystals which had separated were filtered off. Recrystallization from pyridine–ethanol afforded *ethyl 7,9-dibromo-2,4-dimethyl-5-oxo[1]benzopyrano[3,4-c]pyridine-1-carboxylate* (2b) (1.4 g, 10%), m.p. 178—179°, $\nu_{max.}$ 1 750 (ring C=O) and 1 730 cm^{-1} (ester C=O), δ (CF_3CO_2H) 1.55 (3 H, t, ester CH_3), 3.10 and 3.20 (each 3 H, s, CH_3), 4.75 (2 H, q, ester CH_2), and 8.30 and 8.70 (each 1 H, s, aromatic) (Found: C, 44.9; H, 2.9; N, 3.2. $C_{17}H_{13}Br_2NO_4$ requires C, 44.8; H, 2.85; N, 3.1%).

Reactions of the Tetrahydropyridine Derivatives (1).—(*a*) To a suspension of (1b) (1.4 g) in acetic acid (10 ml), ethanol (2 ml) was added, and the mixture was boiled under reflux for 0.5 h. The solid that separated on cooling was recrystallized from ethanol–water giving the *4-hydroxy-compound* (3) (0.9 g), m.p. 163—164° (decomp.), $\nu_{max.}$ 3 460 (OH), 3 270 (NH), and 1 660 cm^{-1} (C=O) (Found: C, 35.9; H, 2.6; Br, 47.6; N, 2.2. $C_{20}H_{17}Br_4NO_5$ requires C, 35.8; H, 2.5; Br, 47.7; N, 2.1%). Heating this product (3) with ammonium acetate in ethanol for 10 min gave back compound (1b).

When the hydroxy-derivative (3) (0.9 g) was dissolved in hot acetic anhydride (2 ml) and the solution kept at room temperature, pale yellow crystals were formed. Recrystallization from dimethyl sulphoxide–ethanol gave the *N-acetyl derivative* (4) (0.6 g), m.p. 190—191° (decomp.), $\nu_{max.}$ 3 460 (OH) and 1 680 cm^{-1} (NAc and ester C=O), δ (C_5D_5N) 1.16 (3 H, t, ester CH_3), 2.05 (3 H, s, NAc), 4.22 (2 H, q, ester CH_2), and 7.40—7.80 (4 H, m, aromatic) (Found: C, 37.1; H, 2.65; Br, 44.7; N, 2.1. $C_{22}H_{19}Br_4NO_6$ requires C, 37.0; H, 2.7; Br, 44.9; N, 2.0%).

Treatment of (3) (0.4 g) with acetic anhydride (1 ml) and pyridine (1 ml) under reflux for 1 h afforded the NOOO-*tetra-acetyl derivative* (5) (0.3 g), m.p. 175—178°, $\nu_{max.}$ 1 775, 1 755 (OAc), 1 710 (ester C=O), and 1 670 cm^{-1} (NAc), δ (C_5D_5N) 2.0 (3 H, s, NAc), 2.14, 2.24, and 2.50 (each 3 H, s, OAc), and 7.70—8.10 (4H, m, aromatic) (Found: C, 39.8; H, 3.0; Br, 38.2; N, 1.7. $C_{28}H_{25}Br_4NO_9$ requires C, 40.0; H, 3.0; Br, 38.1; N, 1.7%).

(*b*) Acetic anhydride (10 ml) and compound (1a) (1.4 g) were heated for 0.5 h. The precipitate was collected and recrystallized from dimethyl sulphoxide–ethanol to afford the *1-acetyl derivative* (6) (1.3 g), m.p. 230—231° (decomp.), $\nu_{max.}$ 3 420 (OH), 3 400, 3 300 (NH_2), and 1 670 cm^{-1} (ester C=O and NAc) (Found: C, 63.2; H, 6.1; N, 6.1. $C_{24}H_{28}N_2O_7$ requires C, 63.1; H, 6.2; N, 6.1%).

A mixture of (1a) (0.5 g) and acetic anhydride (2 ml) in pyridine (2 ml) was boiled under reflux for 3 h, then left to cool overnight; pale yellow crystals separated. Recrystallization from ethanol gave the NNOO-*tetra-acetyl derivative* (7a) as white crystals (0.6 g), m.p. 205—207°, $\nu_{max.}$ 3 220 (NH), 1 770 (OAc), 1 710 (NHAc), and 1 680 cm^{-1} (ester

C=O and NAc) (Found: C, 61.9; H, 5.7; N, 4.8. $C_{30}H_{34}N_2O_{10}$ requires C, 61.85; H, 5.8; N, 4.8%). Similar treatment of (1b) (0.8 g) gave the *tetra-acetyl derivative* (7b) (0.8 g), which crystallized from acetic acid as white needles, m.p. 257—258° (decomp.), $\nu_{max.}$ 3 230 (NH), 1 775 (OAc), 1 705 (NHAc), and 1 680 cm^{-1} (NAc and ester C=O) (Found: C, 39.9; H, 3.3; Br, 38.4; N, 3.45. $C_{28}H_{26}Br_4N_2O_8$ requires C, 40.1; H, 3.1; Br, 38.2; N, 3.3%).

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