[Chem. Pharm. Bull. 25(7)1607—1609(1977)]

UDC 547.829.04 : 547.464.2-931.04

Decarboxylation Reactions. VI.[1] Reaction of α-Arylmethyleneamino-substituted Derivatives of Pyridine, Quinoline, and Isoquinoline with Trichloroacetic Anhydride

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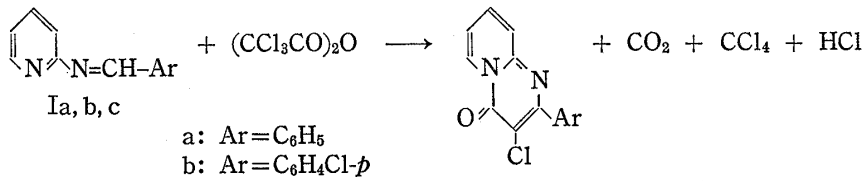
(Received October 18, 1976)

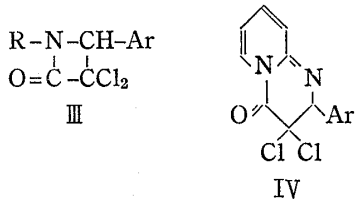
A new one step chloropyrimidinone ring-closure of the conjugated –N=C(Cl)–N=CH– system of α-arylmethyleneamino-substituted derivatives of pyridine, quinoline, and isoquinoline has been achieved by allowing them to react with trichloroacetic anhydride.

Keywords——pyrimidinone ring-closure; decarboxylation reaction; trichloroacetic anhydride; chlorine cation extraction; benzylideneamino derivatives

It has been reported in an earlier paper[3] that the reaction of Schiff bases of N-benzylideneamine type with trichloroacetic anhydride proceeds with decarboxylation to give 3,3-dichloro-2-azetidinones. We now wish to disclose a new reaction of the conjugated –N=C(Cl)–N=CH– system of heterocyclic azines with trichloroacetic anhydride, affecting chloropyrimidinone ring-closure. The reaction was first realized by allowing 2-(benzylideneamino)-pyridine (Ia) to react with trichloroacetic anhydride. The reaction proceeded with decarboxylation on heating at 100—105° in toluene to give 3-chloro-2-phenyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (IIa) as prisms, mp 162—163°, in 33% yield. Identity of this material was made, in the main, on the basis of elemental analysis and ultraviolet (UV) spectral measurement. Its melting point and UV spectral data are in well agreement with those previously reported.[4] With two extended experiments the reaction is represented as in the following equation. As a side product carbon tetrachloride was confirmed by gas-liquid chromatographic analysis of the reaction solution.



When considered pathway of the reaction by analogy with that of the previously reported 3,3-dichloro-2-azetidinone (III) formation, a six-membered intermediate (IV) is supposed as a precursor of IIa,b,c, into which conversion is affected by elimination of hydrogen chloride from IV. The path of the formation of IV is essentially similar to that of the 3,3-dichloro-2-



1) Part V: O. Iwamoto, K. Suzuki, Y. Terao, and M. Sekiya, *Chem. Pharm. Bull.* (Tokyo), **24**, 2409 (1976).
2) Location: *2-2-1, Oshika, Shizuoka.*
3) M. Sekiya and T. Morimoto, *Chem. Pharm. Bull.* (Tokyo), **23**, 2353 (1975).
4) The material, mp 164°, synthesized by another route, was first reported in 1925 with an incorrect structure [O. Seide, *Chem. Ber.*, **58**, 352 (1925)] and later was assigned as IIa based on UV spectral data [R. Adams and I.J. Pachter, *J. Am. Chem. Soc.*, **74**, 5495 (1952)].

azetidinone formation, but the initial electrophilic attack of trichloroacetyl is directed not at imino nitrogen as in the latter but at pyridino nitrogen. Thus, the mechanism of the reaction may be deduced as shown in Chart 1, where trichloroacetyl attacks at pyridino nitrogen and then, chlorine cation extraction from the resulting N-trichloroacetyl, followed by the pyrimidinone ring-closure, is affected by the attack of trichloromethyl anion formed through decarboxylation of trichloroacetate anion.

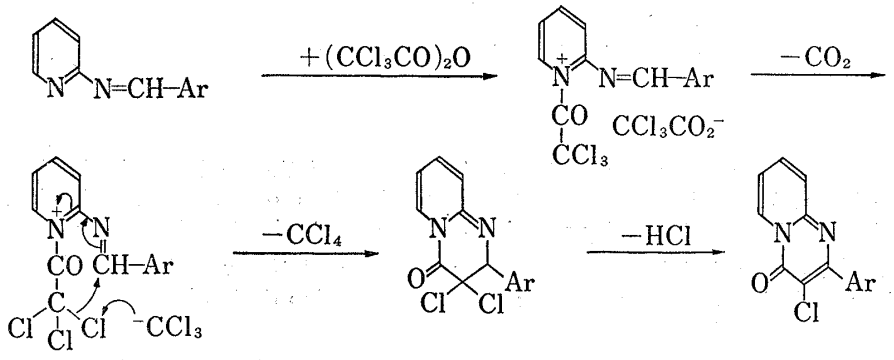
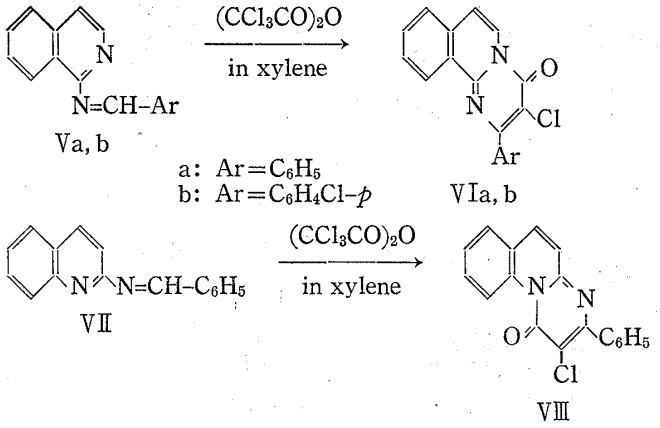


Chart 1

A finding of the above 2-aryl-3-chloro-4*H*-pyrido[1,2-*a*]-pyrimidin-4-one formation was extended by allowing N-benzylideneamino derivatives (Va,b, VII) of isoquinoline and quinoline to react with trichloroacetic anhydride, whereupon a new series of chloropyrimidinone derivatives (VIa,b, VIII) were obtained. Thus, the present work has provided an useful means of one step chloropyrimidinone ring-closure.



Experimental

All melting and boiling points are uncorrected. Infrared (IR) and UV spectra were recorded on a Hitachi EPI-G2 spectrophotometer and a Hitachi EPS-3T spectrophotometer, respectively. Nuclear magnetic resonance (NMR) spectra were taken at 60 MHz with a Hitachi R-24 spectrometer using tetramethylsilane as an internal standard.

α-Arylmethyleneamino-substituted Derivatives of Pyridine, Isoquinoline, and Quinoline——2-(Arylmethyleneamino)pyridines (Ia, b, c): 2-(Benzylideneamino)pyridine (Ia), bp 137—138° (1.9 mmHg) [lit.,[5] bp 200° (18 mmHg), lit.,[6] bp 174—185° (22 mmHg), lit.,[7] bp 184—188° (18 mmHg)], was prepared from 2-aminopyridine and benzaldehyde according to the previously reported method.[5,6] By the same procedure were prepared 2-[(*p*-chlorobenzylidene)amino]pyridine (Ib), mp 92—94°, bp 149—150° (0.9 mmHg) [lit.,[6] bp 122.5—125° (0.5 mmHg)], and 2-[(*p*-methoxybenzylidene)amino]pyridine (Ic), mp 55—57.5°, bp 150—152° (0.5 mmHg) [lit.,[6] mp 55—57.5°, lit.,[6] bp 147—148° (0.6 mmHg)].

5) A. Kirpal and E. Reiter, *Chem. Ber.*, **60**, 664 (1927).
6) I.A. Kaye and I.C. Kogon, *Rec. Trav. Chim.*, **71**, 309 (1952).
7) F.J. Villani, M.S. King, and D. Papa, *J. Am. Chem. Soc.*, **73**, 5916 (1951).

1-(Arylmethyleneamino)isoquinolines (Va, b): 1-(Benzylideneamino)isoquinoline (Va) [yield, 86%. yellow prisms (hexane), mp 68—70°] and 1-[(*p*-chlorobenzylidene)amino]isoquinoline (Vb) [yield, 90%. yellow needles (toluene), mp 136—136.5°] were prepared by refluxing toluene solutions of 1-aminoisoquinoline (0.1 mol) and the corresponding aldehydes (0.2 mol) for 15 hr under distillation of toluene-water azeotrope.

2-(Benzylideneamino)quinoline (VII): By the same procedure as described above, VII was prepared from 2-aminoquinoline and benzaldehyde as yellow prisms (isopropyl ether), mp 74—74.5°, in 66% yield.

General Procedures for the Reaction of α-Arylmethyleneamino-substituted Derivatives of Pyridine, Isoquinoline, and Quinoline with Trichloroacetic Anhydride——To a solution of 0.03 mol each of Ia, b, c in dry toluene (30 ml) was added 0.039 mol of trichloroacetic anhydride, and the mixture was heated with constant stirring at the temperature effecting considerable evolution of CO_2. In the runs of Va, b and VII xylene was used in place of toluene. Process of the reaction was checked by passing dry air free from CO_2 through the reaction vessel into aq. $Ba(OH)_2$. In the runs of Ia, b, c the reaction solution was concentrated under reduced pressure. The residue was triturated with EtOH and the resulting crystals of 2-aryl-3-chloro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (IIa, b, c) were collected by filtration. In the runs of Va, b and VII most of the product, 2-aryl-3-chloro-4*H*-pyrimido[2,1-*a*]isoquinolin-4-one (VIa, b) or 2-chloro-3-phenyl-1*H*-pyrimido[1,2-*a*]quinolin-1-one (VIII), deposited as crystals in the reaction solution. The crystals were collected by filtration after cooling and the filtrate was worked up by the same procedure as described above. The products obtained by the above procedures were recrystallized from appropriate solvents.

3-Chloro-2-phenyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (IIa): Obtained by the reaction of Ia (100—105° for 1.5 hr). Yield, 33%. Pale yellow needles (EtOH), mp 162—163° (lit.,[4] mp 164°). *Anal.* Calcd. for $C_{14}H_9ClN_2O$: C, 65.50; H, 3.53; N, 10.92. Found: C, 65.80; H, 3.59; N, 10.71. IR ν_{max}^{KBr} cm^{-1}: 1693 (C=O), 1632 (C=N). UV λ_{max}^{EtOH} mμ (ε): 266 (19500), 353 (11500). NMR δ (in $CDCl_3$): 7.08 (1H, ddd, J=7.3, 4.0, 1 Hz, $H_{(7)}$), 8.93 (1H, ddd, J=7.3, 1.5, 1 Hz, $H_{(6)}$), 7.3—7.9 (7H, m, other H).

3-Chloro-2-(*p*-chlorophenyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (IIb): Obtained by the reaction of Ib (103—105° for 2 hr). Yield, 37%. Pale yellow needles (anisole), mp 258—259°. *Anal.* Calcd. for $C_{14}H_8Cl_2N_2O$: C, 57.76; H, 2.77; N, 9.62. Found: C, 57.80; H, 2.68; N, 9.69. IR ν_{max}^{KBr} cm^{-1}: 1691 (C=O), 1628 (C=N). UV λ_{max}^{EtOH} mμ (ε): 275 (20900), 354 (10000), 360 (infl. 9710). NMR δ (in CF_3CO_2H): 7.76 (4H, s, C_6H_4Cl), 7.6—8.8 (3H, m, $H_{(7)}$, $H_{(8)}$, $H_{(9)}$), 9.49 (1H, *ca.*d, J=7 Hz, $H_{(6)}$).

3-Chloro-2-(*p*-methoxyphenyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (IIc): Obtained by the reaction of Ic (80—85° for 2.5 hr). Yield, 23%. Pale yellow needles (EtOH), mp 175—175.5°. *Anal.* Calcd. for $C_{15}H_{11}ClN_2O_2$: C, 62.83; H, 3.87; N, 9.77. Found: C, 62.89; H, 3.86; N, 9.87. IR ν_{max}^{KBr} cm^{-1}: 1692 (C=O), 1630 (C=N). UV λ_{max}^{EtOH} mμ (ε): 303 (25200), 351 (9710), 364 (infl. 9920). NMR δ (in $CDCl_3$): 3.85 (3H, s, CH_3), 7.00 (2H, d, J=9.0 Hz) and 7.73 (2H, d, J=9.0 Hz, C_6H_4), 6.9—7.3 (1H, m, $H_{(7)}$), 7.6—8.0 (2H, m, $H_{(8)}$, $H_{(9)}$), 9.00 (1H, *ca.*d, J=7 Hz, $H_{(6)}$).

3-Chloro-2-phenyl-4*H*-pyrimido[2,1-*a*]isoquinolin-4-one (VIa): Obtained by the reaction of Va (115—117° for 2 hr). Yield, 65%. Pale yellow needles (toluene), mp 217—218.5°. *Anal.* Calcd. for $C_{18}H_{11}Cl_2N_2O$: C, 70.48; H, 3.61; N, 9.13. Found: C, 70.22; H, 3.64; N, 9.28. IR ν_{max}^{KBr} cm^{-1}: 1694 (C=O), 1646 (C=N). UV λ_{max}^{EtOH} mμ (ε): 226 (28500), 271 (23400), 284 (24500), 299.5 (22500), 349 (7060), 366 (13300), 384 (13100). NMR δ (in $CDCl_3$): 7.34 (1H, d, J=8.0 Hz, $H_{(7)}$), 8.80 (1H, d, J=8.0 Hz, $H_{(6)}$), 8.90—9.10 (1H, m, $H_{(11)}$), 8.00—8.20 (2H, m) and 7.5—7.9 (6H, m, other H).

3-Chloro-2-(*p*-chlorophenyl)-4*H*-pyrimido[2,1-*a*]isoquinolin-4-one (VIb): Obtained by the reaction of Vb (117—120° for 4 hr). Yield, 67%. Pale yellow needles (toluene), mp 262.5—263°. *Anal.* Calcd. for $C_{18}H_{10}Cl_2N_2O$: C, 63.36; H, 2.95; N, 8.21. Found: C, 63.51; H, 3.05; N, 8.32. IR ν_{max}^{KBr} cm^{-1}: 1703 (C=O), 1643 (C=N). UV λ_{max}^{EtOH} mμ (ε): 227.5 (28800), 247 (11300), 253.5 (13200), 259.5 (18000), 274 (infl. 25700), 286 (27800), 300 (24500), 350 (6920), 367 (13200), 386 (13000). NMR δ (in CF_3CO_2H): 7.67 (4H, s, C_6H_4Cl), 8.07 (1H, d, J=7.7 Hz, $H_{(7)}$), 7.95—8.3 (3H, m, $H_{(8)}$, $H_{(9)}$, $H_{(10)}$), 8.95 (1H, *ca.*d, J=8 Hz, $H_{(11)}$), 9.12 (1H, d, J=7.7 Hz, $H_{(6)}$).

2-Chloro-3-phenyl-1*H*-pyrimido[1,2-*a*]quinolin-1-one (VIII): Obtained by the reaction of VII (117—120° for 1.2 hr). Yield, 64%. Pale yellow needles (BuOH), mp 184—185°. *Anal.* Calcd. for $C_{15}H_{11}ClN_2O$: C, 70.48; H, 3.61; N, 9.13. Found: C, 70.41; H, 3.68; N, 9.23. IR ν_{max}^{KBr} cm^{-1}: 1670 (C=O), 1631 (C=N). UV λ_{max}^{EtOH} mμ (ε): 237 (20400), 254 (23400), 279 (28000), 358 (infl. 7460), 373 (11200), 390 (8970). NMR δ (in $CDCl_3$): 9.80—10.05 (1H, m, $H_{(10)}$), 7.45—8.10 (10H, m, other H).

Acknowledgement The authors are indebted to the members of Analysis Center of this college for microanalyses.