Anal. Calcd. for $C_6H_{11}N_5$: C, 46.43; H, 8.44; N, 45.13. Found: C, 46.36; H, 8.51; N, 45.17.

1-(2-Diethylaminoethyl)tetrazole. In the manner just described, 12.2 g. of 2-diethylaminoethyl isocyanide was treated with hydrogen azide; the reaction mixture stayed as one phase. The benzene and excess hydrogen azide were distilled off, and further distillation gave 11.2 g. (69%) of a pale yellow liquid, b.p. 128–132° at 0.3 mm.

Anal. Calcd. for $C_7H_{15}N_5$: C, 49.68; H, 8.93; N, 41.39. Found: C, 49.43; H, 8.67; N, 41.53.

ANN ARBOR, MICH.

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

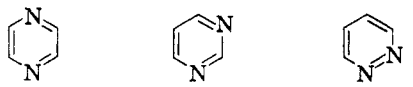
Some Diazine-*N*-oxides[1]

C. F. KOELSCH AND WILLIAM H. GUMPRECHT

Received May 26, 1958

Preparations of mono- and di-*N*-oxides of pyrazine, 2-methylpyrazine, and 2,5-dimethylpyrazine, and of mono-*N*-oxides of pyrimidine and pyridazine are described. The oxides of methylated pyrazines undergo normal Boekelheide rearrangement with acetic anhydride, forming acetoxymethylpyrazines, but all of the oxides were resistant to nitration. A strong absorption at 1230–1325 cm.$^{-1}$ appears to be characteristic of the *N*-oxide function.

Heteroaromatic *N*-oxides have been studied extensively in recent years,[2] but little is known about the *N*-oxides of simple diazines.[3] Preparations and a few reactions of some of these substances are described in the present paper.



I II III

Pyrazine (I), 2-methylpyrazine, and 2,5-dimethylpyrazine yielded mainly mono-oxides when treated with one equivalent of hydrogen peroxide in hot acetic acid. As expected, two isomeric mono-oxides of 2-methylpyrazine were formed. In each preparation, small amounts of the corresponding dioxides were also produced, and these compounds were obtained in good yields when excess hydrogen peroxide was used.

Pyrimidine (II) was destroyed by hydrogen peroxide in hot acetic acid, but at room temperature it furnished 6.5% of its mono-oxide (m.p. 95–96°) together with 2.5% of 4(3) pyrimidone; a di-oxide could not be obtained. The yield (11%) and m.p. (85–88°) of pyrimidine mono-oxide reported recently[3j] were not duplicated, but the product obtained in the present work had the same infrared absorption as that described.

Pyridazine (III) gave only a mono-oxide, the best yield being obtained by oxidation at room temperature.

2,5-Dimethylpyrazine mono-oxide formed 1:1 addition products with hydrogen chloride, methyl iodide, or benzyl chloride. Spectral studies did not permit a definite decision as to the point of attachment of the electrophilic reagent, but basification of the benzyl chloride adduct gave no benzaldehyde, indicating that salt formation had involved the unoxidized nitrogen atom. A similar conclusion regarding salt formation was reached by Landquist[3h] in his study of quinoxaline mono-oxide.

2,5-Dimethylpyrazine mono-oxide reacted with acetic anhydride to form 2-acetoxymethyl-5-methylpyrazine, the product expected by analogy with Boekelheide's work in the pyridine series.[4] The same substance, together with 2,5-bisacetoxymethylpyrazine was obtained from 2,5-dimethylpyrazine dioxide. 2-Acetoxymethyl-5-methylpyrazine dioxide was partly deoxidized by acetic anhydride, giving 2,5-bisacetoxymethylpyrazine and its mono-oxide and 2-acetoxymethyl-5-methylpyrazine mono-oxide.

Assignment of structures to the two isomeric mono-oxides of 2-methylpyrazine was based on reactions with acetic anhydride. 2-Methylpyrazine-1-oxide (m.p. 43–45°) gave an acetate saponified to 2-hydroxymethylpyrazine, which showed strong broad —OH absorption at 3300 cm.$^{-1}$ 2-Methylpyrazine-4-oxide (m.p. 91–92°) gave an acetate saponified to 5-methyl-2(1)-pyrazinone, showing weak absorption at 1660 cm.$^{-1}$

Corresponding to observations of Adams and Miyano[5] in the pyridine series, 2,5-dimethylpyra-

(1) From the Ph.D. thesis of W. H. Gunprecht, July 1957.

(2) C. C. J. Culvenor, *Revs. Pure and Appl. Chem. (Australia)*, **3**, 83 (1953); E. Ochiai, *J. Org. Chem.*, **18**, 534 (1953); A. R. Katritzky, *Quart. Revs.*, **10**, 395 (1956); M. Colonna, *Bull. sci. soc. chim. ind. Bologna*, **15**, 1 (1957).

(3) (a) E. Ochiai, M. Ishikawa, and S. Zai-Ren, *J. Pharm. Soc. Japan*, **65**, 73 (1945); (b) G. T. Newbold and F. S. Spring, *J. Chem. Soc.*, 1183 (1947); (c) R. A. Baxter, G. T. Newbold, and F. S. Spring, *J. Chem. Soc.*, 1859 (1948); (d) W. Sharp and F. S. Spring, *J. Chem. Soc.*, 932 (1951); (e) G. T. Newbold, W. Sharp, and F. S. Spring, *J. Chem. Soc.*, 2679 (1951); (f) E. Ochiai and H. Yamonaka, *Pharm. Bull. (Tokyo)*, **3**, 175 (1955); (g) W. F. Beech, *J. Chem. Soc.*, 3094 (1955); (h) J. K. Landquist, *J. Chem. Soc.*, 1885 (1956); (i) G. Karmas and P. E. Spoeri, *J. Am. Chem. Soc.*, **78**, 4071 (1956); (j) R. H. Wiley and S. C. Slaymaker, *J. Am. Chem. Soc.*, **79**, 2233 (1957).

(4) V. Boekelheide and W. J. Linn, *J. Am. Chem. Soc.*, **76**, 1286 (1954).

(5) R. Adams and S. Miyano, *J. Am. Chem. Soc.*, **76**, 3168 (1954).

zine dioxide reacted with benzaldehyde in presence of sodium hydroxide, whereas dimethylpyrazine itself was not affected; the product was 2,5-distyrylpyrazine dioxide. Strangely, 2,5-dimethylpyrazine mono-oxide yielded 2,5-distyrylpyrazine mono-oxide, and no evidence for superior reactivity of one of the methyl groups was obtained.

Nitration of 2,5-dimethylpyrazine dioxide could not be accomplished. The compound was recovered quantitatively after it had been kept for one hour at 50° with sodium nitrate in excess sulfuric acid; and 75% of it was recovered after 16 hr. at 70° with the same reagent.

Infrared absorption of *N*-oxides has been found by Clemo and Daglish[6] in the regions 1350–1390 and 1040–1090 cm.$^{-1}$, whereas Sartori, Costa, and Blasina[7] found it in the region 1240–1310 cm.$^{-1}$ Observations in the present work agree with the latter assignment only. All of the oxides examined showed an absorption band, usually strong, at 1230–1325 cm.$^{-1}$, which was absent in the spectrum of the parent diazine.

EXPERIMENTAL

Pyrazine mono-oxide. A solution of 14.2 g. of 30% hydrogen peroxide in 100 ml. of acetic acid was added dropwise during 2.5 hr. to a solution of 10 g. of pyrazine in 125 ml. of acetic acid at 70–80°. Heating was continued for about 5 hr. or until starch-iodide showed no peroxide. Acetic acid was then removed by distilling at 100° under reduced pressure, adding 200 ml. of water, and repeating the distillation. The residue was dissolved in 500 ml. of hot chloroform and dried with a mixture of sodium sulfate and sodium carbonate. Concentration of the solution to 150 ml. gave a small amount of crude dioxide, and more of this (0.6 g.) was obtained by exhaustive extraction of the drying agents.

Evaporation of the chloroform left 8.6 g. of crude mono-oxide, and recrystallization from benzene gave the pure compound; colorless needles, m.p. 113–114°; strong absorption at 1305 cm.$^{-1}$ ($CHCl_3$).

Anal. Calcd. for $C_4H_4N_2O$: C, 50.0; H, 4.2; N, 29.16. Found: C, 50.3; H, 4.2; N, 28.4.

Pyrazine dioxide. Oxidation of 5 g. of pyrazine in 40 ml. of acetic acid with 14.3 g. of 30% hydrogen peroxide at 70° for 24 hr. gave 6.3 g. of crude solid product. Soxhlet extraction with 60–68° ligroin removed 2.76 g. of mono-oxide, and crystallization of the residue gave 2.97 g. of pure dioxide, colorless needles from methanol, m.p. 285–295°; strong absorption at 1270 cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_4H_4N_2O_2$: C, 42.8; H, 3.6; N, 25.0. Found: C, 42.7; H, 3.7; N, 24.6.

2-Methylpyrazine oxides. Oxidation of 22.5 g. of 2-methylpyrazine in 275 ml. of acetic acid with 26 g. of 35% hydrogen peroxide at 70–80° for 8 hr. gave 24 g. of yellow oil which slowly crystallized. Soxhlet extraction with 30–40° ligroin left 2.2 g. of crude 2-methylpyrazine dioxide which was purified by sublimation at 140° and 0.1 mm. It formed colorless needles, m.p. 230–231°; strong absorption at 1260 cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_5H_6N_2O_2$: C, 47.6; H, 4.8; N, 22.2. Found: C, 47.8; H, 4.8; N, 22.1.

Evaporation of the ligroin extract left 18.7 g. of mixed mono-oxides. These were separated by fractional distillation followed by crystallization from ether. The first fraction (9.15 g., b.p. 114–116° at 7 mm.) gave 4.85 g. of *2-methylpyrazine-4-oxide;* large colorless prisms, m.p. 91–92°; strong absorption at 1300 cm.$^{-1}$ ($CHCl_3$).

Anal. Calcd. for $C_5H_6N_2O$: C, 54.5; H, 5.5. Found: C, 54.5; H, 5.6.

The second fraction (4.9 g., b.p. 109–110° at 5 mm.) was combined with the material in the mother liquor from the 4-oxide and crystallized several times, giving 5.7 g. of *2-methylpyrazine-1-oxide,* fine needles, m.p. 43–45°; strong absorption at 1305 cm.$^{-1}$ ($CHCl_3$). A mixture of the isomeric mono-oxides had m.p. 41–85°.

Anal. Calcd. for $C_5H_6N_2O$: C, 54.5; H, 5.5; N, 25.4. Found: C, 54.5; H, 5.4; N, 25.2.

Reaction of 2-methylpyrazine-1-oxide with acetic anhydride. A mixture of 3.6 g. of the oxide with 10 ml. of acetic anhydride was boiled for 30 min. and then kept at room temperature for 3 days. Evaporation at 100° under reduced pressure left a viscous black residue which was distilled at 10 mm., giving 2.9 g. of an orange oil. A solution of this crude acetate in 30 ml. of 10% sodium hydroxide was kept under nitrogen for three days, then neutralized with carbon dioxide and evaporated. Extraction with chloroform and distillation gave 1.7 g. of 2-hydroxymethylpyrazine, a colorless oil, b.p. 64–66° at 0.3 mm. The ultraviolet spectrum (95% alcohol) had bands at 2200 Å, ϵ = 4200, and 2650 A, ϵ = 7300, with a shoulder at about 3000 Å, ϵ = 1100.

Anal. Calcd. for $C_5H_6N_2O$: C, 54.5; H, 5.5. Found: C, 54.7; H, 5.7.

Reaction of 2-methylpyrazine-4-oxide with acetic anhydride. A mixture of 4.5 g. of the oxide with 10 ml. of acetic anhydride was processed as described for the isomeric oxide. There was obtained 3.0 g. of crude distilled acetate, and hydrolysis of this gave 1.9 g. of 5-methyl-2(1)-pyrazinone, colorless needles from ether, m.p. 68–69°. The compound gave no color with ferric chloride; its ultraviolet spectrum (95% alcohol) had bands at 2220 Å, ϵ = 13000, and 2700 Å, ϵ = 12600.

Anal. Calcd. for $C_5H_6N_2O$: C, 54.5; H, 5.5. Found: C, 54.6; H, 5.7.

2,5-Dimethylpyrazine mono-oxide. A solution of 132 g. of 2,5-dimethylpyrazine and 132 ml. of 30% hydrogen peroxide in 3 liters of acetic acid was kept at 70–80° for 9 hr. and then evaporated under reduced pressure. Soxhlet extraction of the residue with 60–68° ligroin left a small amount of insoluble dioxide; the soluble part was recrystallized from 2-propanol giving 90 g. of the mono-oxide, colorless needles, m.p. 105–106° (reported[2b] 105–108°); strong absorption at 1285 cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_6H_8N_2O$: C, 58.0; H, 6.5; N, 22.6. Found: C, 58.1; H, 6.6; N, 22.5.

Evaporation of a solution of the mono-oxide in concentrated hydrochloric acid left 2,5-dimethylpyrazinium chloride *N*-oxide, which had m.p. 166–168° after repeated crystallization from alcohol. The spectrum (Nujol) had strong bands at 1900, 2000, 2200, and 2300 cm.$^{-1}$ similar to those of 2,5-dimethylpyrazinium chloride, and one at 1800 cm.$^{-1}$

Anal. Calcd. for $C_6H_9ClN_2O$: C, 44.9; H, 5.7; N, 17.4. Found: C, 45.4; H, 5.9; N, 17.3.

The spectrum of *N*-hydroxy-4-picolinium chloride (colorless needles from alcohol; m.p. 120–122°; found: C, 49.7; H, 5.5; N, 9.4; C_6H_8ClNO requires: C, 49.5; H, 5.5; N, 9.6) had a broad strong band at 1700–2500 cm.$^{-1}$, not at all similar to the two spectra referred to above.

1,2,5-Trimethylpyrazinium iodide N-oxide, obtained in 71% yield from 18 g. of the mono-oxide and 21 g. of methyl iodide in 30 ml. of dimethylformamide, formed yellow plates from alcohol, dec. 234–237°.

Anal. Calcd. for $C_7H_{11}INO_2$: C, 31.6; H, 4.2; N, 10.6. Found: C, 31.8; H, 4.4; N, 10.8.

1,2,5-Trimethylpyrazinium chloride N-oxide, from the iodide with silver chloride in water, formed colorless plates from alcohol-ether, dec. 190°.

(6) G. R. Clemo and A. F. Daglish, *J. Chem. Soc.,* 1481 (1950).

(7) G. Sartori, G. Costa, and P. Blasina, *Gazz. chim. ital.,* 85, 1085 (1955).

Anal. Calcd. for $C_7H_{11}ClN_2O$: C, 48.2; H, 6.4; N, 16.0. Found: C, 48.0; H, 6.7; N, 15.9.

The methochloride-oxide was recovered unchanged after 8 hr. treatment with excess hydrogen peroxide in acetic acid at 80°.

1-Benzyl-2,5-dimethylpyrazinium chloride N-oxide, from the mono-oxide and excess benzyl chloride, kept at 60° for one week, formed colorless plates from alcohol, dec. 210–220°. No benzaldehyde was formed when this salt was warmed with aqueous alkali.

Anal. Calcd. for $C_{13}H_{15}ClN_2O$: C, 62.2; H, 6.0; N, 11.2. Found: C, 62.3; H, 6.1; N, 11.2.

Attempted nitration of 1 g. of 2,5-dimethylpyrazine mono-*N*-oxide in 5 ml. of sulfuric acid containing 0.7 g. of sodium nitrate by heating for 1 hr. at 70° gave back 0.92 g. of unchanged oxide. Using 1.4 g. of sodium nitrate and prolonging the heating to 14 hr. gave back 0.7 g. of oxide.

2,5-Distyrylpyrazine mono-N-oxide was obtained in a yield of 20% when a mixture of 5 g. of 2,5-dimethylpyrazine mono-oxide, 4.3 g. of benzaldehyde, one ml. of 5% sodium hydroxide, and 50 ml. of alcohol was kept at 60–70° for one week under nitrogen. It formed yellow needles from acetic acid, m.p. 243–245°. A mono-styryl derivative could not be isolated from this or several other experiment using piperidine or triethylamine as catalysts.

Anal. Calcd. for $C_{20}H_{16}N_2O$: C, 80.0; H, 5.4; N, 9.3. Found: C, 79.7; H, 5.5; N, 9.2.

Reaction of 2,5-dimethylpyrazine mono-N-oxide with acetic anhydride. A mixture of 50 g. of the oxide with 100 ml. of acetic anhydride was warmed under reflux until vigorous reaction started, and after this was over the black mixture was boiled for 1 hr. Acetic acid and anhydride were then removed under reduced pressure and the residue was distilled, giving 24 g. of light yellow oil and a carbonaceous residue. Redistillation gave mainly 2-acetoxymethyl-5-methylpyrazine, b.p. 70–71°, at 0.4 mm.; n_D^{25} 1.5057.

Anal. Calcd. for $C_8H_{10}N_2O_2$: C, 57.8; H, 6.1; N, 16.9. Found: C, 57.5; H, 6.1; N, 17.0.

Saponification of 1 g. of the ester with 10 ml. of 10% sodium hydroxide under nitrogen at room temperature for two days, and exhaustive extraction with ether gave 2-hydroxymethyl-5-methylpyrazine; purified by microdistillation at 0.5 mm., the compound had m.p. 36–39°.

Anal. Calcd. for $C_6H_8N_2O$: C, 58.0; H, 6.5; N, 22.6. Found: C, 58.0; H, 6.6; N, 22.6.

2-Acetoxymethyl-5-methylpyrazine di-N-oxide was obtained in 80% yield when a solution of 3 g. of 2-acetoxymethyl-5-methylpyrazine and 5 ml. of 30% hydrogen peroxide in 30 ml. of acetic acid was kept at 80° for 10 hr. It formed colorless plates from alcohol, m.p. 242–243°.

Anal. Calcd. for $C_8H_{10}N_2O_4$: C, 48.5; H, 5.1; N, 14.1. Found: C, 48.3; H, 5.3; N, 141.1

Hydrolysis of the ester with 0.1% sulfuric acid by keeping under nitrogen for one month gave 55% of 2-hydroxymethylpyrazine di-*N*-oxide, colorless plates from alcohol, m.p. 226–228°.

Anal. Calcd. for $C_6H_8N_2O_3$: C, 46.2; H, 5.2; N, 17.9. Found: C, 46.6; H, 5.2; N, 17.9.

Reaction of 2-acetoxymethyl-5-methylpyrazine di-N-oxide with acetic anhydride. A mixture of 31.5 g. of the dioxide with 53 ml. of acetic anhydride was treated in the same way as described for the mono-oxide acetylation. The crude distillate (23.7 g.) crystallized when it was cooled. Recrystallization from alcohol gave 5.3 g. of *2,5-diacetoxymethylpyrazine mono-N-oxide,* colorless needles, m.p. 113–114°.

Anal. Calcd. for $C_{10}H_{12}N_2O_5$: C, 50.0; H, 5.0; N, 11.7. Found: C, 50.0; H, 5.3; N, 11.9.

Redistillation of the material in the alcoholic mother liquor followed by chromatography on alumina gave 1.2 g. of 2,5-diacetoxymethylpyrazine, m.p. 80–81° (see below) and 1.1 g. of a *mono-N-oxide of 2-acetoxymethyl-5-methylpyrazine,* colorless needles from ether, m.p. 96–97°.

Anal. Calcd. for $C_8H_{10}N_2O_3$: C, 52.7; H, 5.5; N, 15.4 Found: C, 53.4; H, 5.7; N, 15.2.

Confirmation for the structure as a mono-oxide was found in the observation that oxidation with hydrogen peroxide in hot acetic acid gave the dioxide m.p. 242–243° also obtained in a different way as described above.

2,5-Dimethylpyrazine di-N-oxide. This substance was obtained in 90% yield by the method of Newbold and Spring.[3b] It was not changed when it was kept at 70° for one week with methyl iodide alone or in dimethyl formamide. It did not react with phenylmagnesium bromide even in hot anisole. It was recovered nearly quantitatively when attempts to nitrate it were made.

When a mixture of 5 g. of the dioxide, 7.6 g. of benzaldehyde, 1 ml. of 5% sodium hydroxide, and 50 ml. of alcohol was kept under nitrogen for three days, there was formed 7.5 g. of *2,5-distyrylpyrazine* di-*N*-oxide, yellow needles from acetic acid, dec. 284–287°.

Anal. Calcd. for $C_{20}H_{16}N_2O_2$: C, 75.9; H, 5.1; N, 8.9. Found: C, 75.8; H, 5.2; N, 8.6.

Distyrylpyrazine dioxide (0.5 g.) boiled in chloroform with 2 ml. of phosphorus trichloride gave 0.3 g. of distyrylpyrazine, yellow plates from benzene, m.p. 218–219° (reported[8] 218–219°). It was found that the compound was converted into a colorless insoluble polymer (?) dec. 331–333° when the solid was exposed for a few hours to ultraviolet light. The polymer was analyzed without purification.

Anal. Calcd. for $(C_{20}H_{16}N_2O_2)$: C, 75.9; H, 5.1; N, 8.9. Found: C, 75.8; H, 5.2; N, 8.6.

Reaction of 2,5-dimethylpyrazine di-N-oxide with acetic anhydride. A mixture of 20 g. of the dioxide with 48 g. of acetic anhydride reacted vigorously and became black when it was heated. It was boiled for 1 hr. and then distilled, giving 15.2 g. of light yellow oil and a carbonaceous residue. Fractionation of the oil gave 3.25 g. of 2-acetoxymethyl-5-methylpyrazine, b.p. 70–72° at 0.3 mm., and 4.92 g. of *2,5-diacetoxymethylpyrazine,* b.p. 123–124° at 0.5 mm., the latter formed colorless plates from ether, m.p. 80–81°.

Anal. Calcd. for $C_{10}H_{12}N_2O_4$: C, 53.6; H, 5.4; N, 12.5. Found: C, 53.5; H, 5.4; N, 12.7.

The diacetoxy compound was saponified when its solution in 10% sodium hydroxide was kept under nitrogen for one week. Exhaustive extraction with ether gave *2,5-dihydroxymethylpyrazine,* colorless needles from chloroform, m.p. 88–89°.

Anal. Calcd. for $C_6H_8N_2O_2$: C, 51.4; H, 5.8; N, 20.0. Found: C, 51.5; H, 6.0; N, 19.9.

Pyrimidine mono-N-oxide. A solution of 6.5 g. of pyrimidine and 9.3 g. of 30% hydrogen peroxide in 150 ml. of acetic acid was kept at room temperature for 15 days and then evaporated under reduced pressure. The oily residue was basified with dilute sodium carbonate (ammonia evolution), evaporated again, and extracted with chloroform in a Soxhlet. Evaporation of the chloroform left a partly crystalline residue which was extracted with hot cyclohexane. The insoluble part (0.2 g.) was 4(3) pyrimidone, m.p. 165–166° (reported[9] 163–165°) and showed an infrared spectrum identical with that reported[10] for this substance. The soluble part (0.5 g.), was pyrimidine mono-*N*-oxide, colorless needles from cyclohexane, m.p. 95–96°; strong absorption at 1260 $cm.^{-1}$ ($CHCl_3$).

Anal. Calcd. for $C_4H_4N_2O$: C, 50.0; H, 4.2; N, 29.2. Found: C, 49.7; H, 4.2; N, 28.9.

Pyridazine mono-N-oxide. A solution of 10.2 g. of pyridazine and 14.5 g. of 30% hydrogen peroxide in 250 ml. of acetic acid was kept at room temperature for four weeks and then evaporated. The residual oil was dissolved in 100 ml. of water, made strongly basic with solid potassium hy-

(8) R. Franke, *Ber.*, **38**, 3726 (1905).

(9) D. J. Brown, *J. Soc. Chem. Ind.*, 69, 353 (1950).

(10) L. N. Short and H. W. Thompson, *J. Chem. Soc.*, 168 (1952).

droxide, and extracted with ether. Distillation at 0.3 mm. gave 9.7 g. of mono-oxide, m.p. 38–39°. Experiments using two equivalents of hydrogen peroxide, or at higher temperatures gave the same mono-oxide in poorer yields. A solution in chloroform showed strong absorption at 1325 cm.$^{-1}$

Anal. Calcd. for $C_4H_4N_2O$: C, 50.0; H, 4.2; N, 29.2' Found: C, 50.4; H, 4.1; N, 29.0.

Pyridazine mono-oxide reacted vigorously with phosphorus oxychloride, but no pure product could be isolated.

MINNEAPOLIS, MINN.

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

Condensation of 3-Acetylcoumarin with Acetone and Amines[1]

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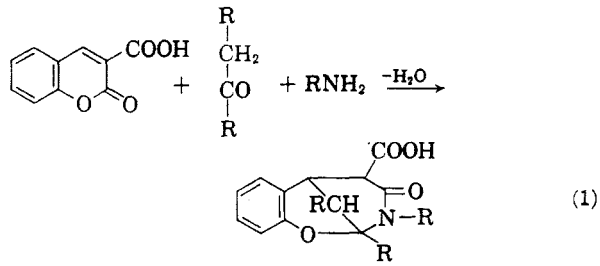
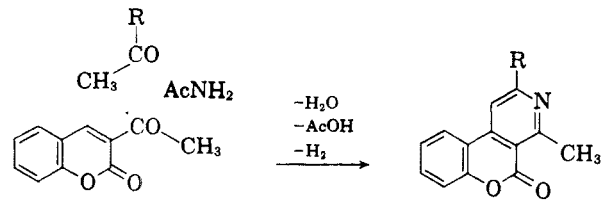
3-Acetylcoumarin reacts with acetone and certain primary amines to form *N*-substituted derivatives of 9-amino-7-methyl-6-dibenzo[*bd*]pyrone, I, in yields of 10–47%.

It has been shown that condensation of 3-coumarincarboxylic acid with ketones and amines yields bridged 8-membered ring compounds.[2]



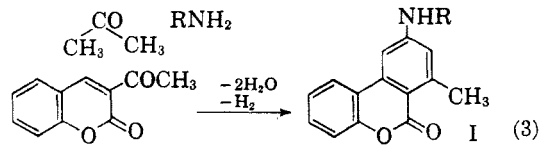
(1)

Further, the reaction of 3-acetylcoumarin with ketones and amides yields pyridocoumarins.[3]



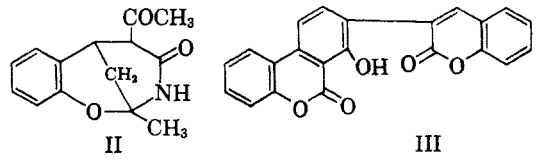
(2)

It has now been found that 3-acetylcoumarin reacts with acetone and amines to form aminobenzocoumarins, I.

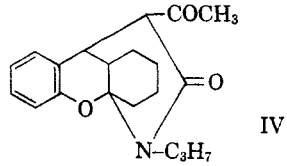


(3)

The amines used were aniline (yield 12.6%), *p*-chloroaniline (15.8%), *n*-butylamine (10.5%), isopropylamine (47%), and cyclohexylamine (40%). Other bases, *t*-butyl, benzyl, and hydroxyethylamine, gave no crystalline products. Ammonia reacted according to (1) forming II, and piperidine yielded III, the self-condensation product of 3-acetylcoumarin.[4]

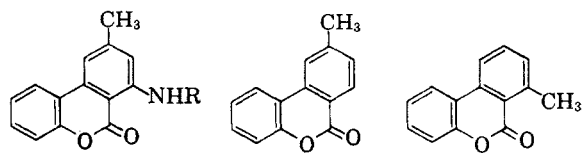


Ketones other than acetone were not thoroughly studied. Diethylketone with isopropylamine gave no crystalline product, whereas cyclohexanone, sterically prevented from forming a compound like I, reacted according to (1) forming IV.



The structures of the products were established by analysis and chemical properties. Although the substances were generally insoluble in dilute aqueous hydrochloric acid, crystalline hydrobromides and acetyl derivatives were formed. The lactone ring in I (R = C_6H_5) was opened when the compound was boiled with alcoholic alkali; acidification of the resulting solution regenerated I, whereas treatment with methyl sulfate gave a methoxy acid and a methoxy ester. Saponification of the ester was difficult but led to the methoxy acid.

That the products were secondary amines of structure I rather than V was proved by degrada-



(1) From the Ph.D. Thesis of H. D. Embree, July 1952.

(2) C. F. Koelsch and M. C. Freerks, *J. Org. Chem.*, **18**, 1538 (1953).

(3) C. F. Koelsch and S. A. Sundet, *J. Am. Chem. Soc.*, **72**, 168 (1950).

(4) C. F. Koelsch and S. A. Sundet, *J. Am. Chem. Soc.*, **72**, 1844 (1950).