3-Benzoyl-2-hydroxy-9-methylpyrido[1,2-*a*]pyrimidin-4-one

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The single aberrant product of the reaction between 2-amino-3-methylpyridine (**2**) and ethyl benzoylacetate (**4**) in diethylbenzene at *ca.* 180° was 3-benzoyl-2-hydroxy-9-methylpyrido-[1,2-*a*]pyrimidin-4-one (**5**). When administered to naive rats, **5** induced behavioral effects strikingly similar to those manifested by morphine-addicted rats who have been deprived of that analgetic.

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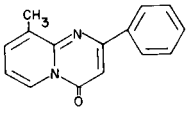
In a recent paper (1), we described the synthesis of 9-methyl-2-phenylpyrido[1,2-*a*]pyrimidin-4-one (**1**) by the reaction between 2-amino-3-methylpyridine (**2**) and ethyl 3-aminocinnamate in diethylbenzene at *ca.* 180°. In an earlier, unsuccessful attempt to prepare **1**, **2** and ethyl benzoylacetate (**4**) were reacted in the same solvent and at the same temperature; the single aberrant product isolated was shown eventually to be 3-benzoyl-2-hydroxy-9-methylpyrido[1,2-*a*]pyrimidin-4-one (**5**). The structure of **5** was deduced from its elemental analyses and from interpretations of its ir, pmr, and mass spectra. There is evidence from the solution spectra that **5** exists as the hydrogen-bonded enolate, and in that form it is the tautomer of **6**, a novel example of a very small group of pyrido[1,2-*a*]pyrimidin-2,4-diones that are to be found in the literature (2). Since the latter class of compounds has invariably been prepared from a 2-aminopyridine and diethyl malonate, there is no precedent for the formation of **5** (or **6**) from the interaction of **2** and **4**. Thus, the mechanism by which that compound was formed remains a matter of speculation. Our recent report (3) that the reaction of 2-acetoacetamidopyridines with phosgene led to the novel 3-aceto-2-chloropyrido[1,2-*a*]pyrimidin-4-ones (**7**), would suggest that a similar cyclization (4) involving a one-carbon fragment insertion mechanism was in operation; however, the mechanism for the latter reaction also remains speculative.



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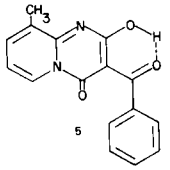

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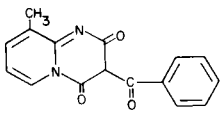

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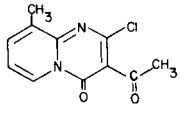

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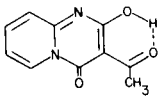

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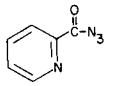

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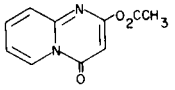

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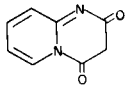

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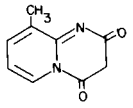

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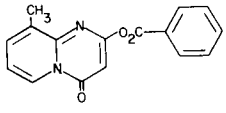

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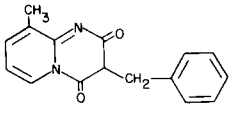

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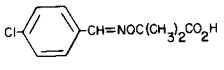

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Kato and Masuda (5) prepared 3-acetyl-2-hydroxypyrido[1,2-*a*]pyrimidin-4-one (**8**) initially, by the reaction of 2-picolinoyl azide (**9**) with diketene, and subsequently, along with 2-acetoxypyrido[1,2-*a*]pyrimidin-4-one (**10**) by the reaction of pyrido[1,2-*a*]pyrimidin-2,4-dione (**11**) with acetyl chloride in sodium ethoxide-benzene. In an attempt to extrapolate the latter procedure, 9-methylpyrido[1,2-*a*]pyrimidin-2,4-dione (**12**) and benzoyl chloride (**13**) were reacted under the same conditions; the only product recovered was ethyl benzoate and unchanged **12**. When **12** and **13** were reacted in potassium bicarbonate-benzene, the exclusive product was the *O*-benzoate (**14**).

Attempts, employing different Lewis-type catalysts, to rearrange **14** to **5** led to the formation of polymeric materials. In addition, attempts to oxidize the 3-benzyl derivative (**15**) to **5** with activated manganese dioxide (6) were also successful.

Normal rats, when treated with **5** developed a rare, bizarre behavioral response. Thus, administered either *ip* or *po*, at doses as low as 25 mpk, the compound induced in that species the "wet-dog shakes syndrome", a response previously associated only with the withdrawal of morphine from animals addicted to that analgetic drug (7). The first report of the elicitation, by a non-related chemical type, of that syndrome in naive, non-morphine-addicted animals, was disclosed only recently by Jahn and Mixich (8), who found that several arylideneaminoxy-substituted aliphatic carboxylic acids, in particular **16**, induced that behavior in normal rats.

Proof of Structure.

The ir spectrum of **5** in deuteriochloroform revealed a weak OH absorption at 3120-3160 cm^{-1} that did not shift upon dilution, along with two carbonyl absorptions at 1720 and 1704 cm^{-1}. The pmr spectrum showed resonances at δ 2.73 (PyCH_3), 7,03 (PyH_5), 7.50-7.65 (5 ArH), 7.77 (PyH_4), 8.04 (PyH_6), and 14.80 (*OH*). The ease of titration with aqueous sodium hydroxide (phenolphthalein, sharp endpoint) confirmed the presence of a strong enolic hydroxyl group. The failure to titrate with perchloric acid in glacial acetic acid was not unexpected, since compounds **7**, **11**, **14**, and **15** also fail to titrate with that reagent. The mass spectrum showed the molecular ion as a major peak at 280.0815 (theory 280.0849) and fragments of m/e 252 (-CO), 175 (-C_6H_5CO), 135 [$C_7H_7N_2O$ (base peak)], and 105 (C_6H_5CO).

Acknowledgement.

The author acknowledges helpful discussions on the structure of **5** with Prof. T. Kato of Tohoku University, Sendai, Japan, and with Drs. M. S. Puar and P. T. Funke of this institute. The elemental analyses and spectra were determined as described in our earlier papers by members of the Analytical Department, while the behavioral studies were performed by members of the CNS Section of the Pharmacology Department, both of this institute.

EXPERIMENTAL

3-Benzoyl-2-hydroxy-9-methylpyrido[1,2-*a*]pyrimidin-4-one (**5**).

A solution of 21.6 g. (0.20 mole) of **2**, 76.8 g. (0.40 mole) of **4**, and 300 ml. of diethylbenzene was heated under nitrogen at 140-145° for 2 hours, the temperature was raised during 1 hour to 180-185°, and kept at that temperature for 1 hour. In the course of the entire heating period, 7.0 ml. of distillate was collected in a Dean-Stark trap attached to the reaction flask. Since no solid separated from the cooled mixture, the solution was concentrated *in vacuo* on the rotary evaporator (90°/10 mm). The residual liquid was distilled, in part, to give 47.2 g. of **4**, b.p. 126-129° (0.7 mm); the viscous oil left in the distillation flask was dissolved in 200 ml. of benzene and poured on a dry-filled column of silica gel (MCB, 200-400 mesh, dried at 100° before use). Elution with seven-150 ml. portions of benzene gave a total of 6.0 g. of additional **4**; elution with fourteen-150 ml. portions of benzene-chloroform (3:1) gave a total of 2.0 g. of an oily solid; and, finally, elution with ten-150 ml. portions of chloroform yielded a total of 3.47 g. of solid. Recrystallization from 100 ml. of ethyl acetate gave 2.00 g. of solid, m.p. 236-238°. This, recrystallized from 50 ml. of acetonitrile gave 1.30 g. of **5**, m.p. 237.5-239.0°; ms: m/e 280.0815 (M^+) (theory 280.0849).

Anal. Calcd. for $C_{16}H_{12}N_2O_3$: C, 67.97; H, 4.27; N, 9.99; N.E., 280 or 0.0. Found: C, 68.39; H, 4.35; N, 10.00; N.E. (aq. sodium hydroxide), 280; N.E. (perchloric acid in acetic acid), 0.0.

9-Methyl-2*H*-pyrido[1,2-*a*]pyrimidin-2,4(3*H*)dione (**12**).

A solution of 30.0 g. (0.27 mole) of 2-amino-3-picoline in 100 ml. of diethyl malonate was heated by means of an oil bath preheated to 150°. Reaction was prompt and ethanol distilled; when the oil bath temperature reached 165°, distillation of ethanol was rapid, and 27 minutes after the initial heating, the mixture turned solid. Distillation of ethanol ceased after 73 minutes at an oil bath temperature of 165°. The total ethanol distillate weighed 25.5 g. (0.55 mole). The cooled mixture was filtered and air-dried to give 62.5 g. of solid; recrystallization from 1250 ml. of *N,N*-dimethylformamide gave 43.9 g. (87% yield) of **12**, m.p. 283-285°, ir (potassium bromide) ν: 2900 (b,m), 2200 (s), 1700 (s), 1600 (b,s), 1510 (s), 1455 (m), 1380 (m), 1350 (s), 1305 (s), 1250 (m) cm^{-1}; pmr (deuteriopyridine) δ: 2.34 (s, 3H, CH_3), 5.85 (2H, CH_2), 6.80 [t (J = 7 Hz), 1H, C$_7H$], 7.40 [d (J = 7 Hz), 1H, C$_8H$], 9.08 [d (J = 7 Hz), 1H, C$_6H$].

Anal. Calcd. for $C_9H_8N_2O_2$: C, 60.87; H, 4.83; N, 15.57; N.E., 0.0. Found: C, 61.01; H, 5.13; N, 15.81; N.E. (perchloric acid), 0.0.

2-(Benzoyloxy)-9-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**14**).

To a stirred suspension of 4.22 g. (0.024 mole) of 9-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-2,4-dione, 4.82 g. (0.048 mole) of dried (100°) potassium bicarbonate, and 100 ml. of anhydrous benzene was added, in 0.25 hour, 6.80 g. (0.1048 mole) of purified benzoyl chloride. Subsequently, the mixture was stirred and heated under reflux for two hours when a clear yellow solution containing a dark sediment had formed. The benzene solution showed a single spot on tlc (silica gel sheet, 100% ethyl acetate), R_f *ca.* 0.71. The hot solution was filtered, the insoluble material was extracted successively with two 10 ml. portions of boiling benzene, the combined benzene solutions were concentrated to dryness *in vacuo*, and the residue, 8.63 g., allowed to crystallize. Recrystallization from 800 ml. of cyclohexane gave 5.11 g. (76% yield) of **14**, m.p. 123-124°; ir (deuteriochloroform): 1750 (s), 1700 (s), 1635 (m), 1590 (m), 1545 (m), 1465 (s), 1430 (w), 1345 (w), 1250 (m) cm^{-1}; pmr (deuteriochloroform) δ: 2.55 (s, 3H, CH_3), 6.28 (s, 1H, C$_3H$), 7.08 [t (J = 7 Hz), 1H, C$_7H$], 7.38-7.80 [m, 5H, C$_8H$ plus 3 Ar-*H* (3,4,5)], 8.20 [q (J = 1.5, 3.0 Hz), 2 Ar-H (2,6)], 8.97 [d (J = 7 Hz), 1H, C$_6H$].

Anal. Calcd. for $C_{16}H_{12}N_2O_3$: C, 58.57; H, 4.32; N, 10.00; N.E., 0.0. Found: C, 58.78; H, 4.36; N, 9.82; N.E. (perchloric acid), 0.0.

9-Methyl-3-benzyl-2*H*-pyrido[1,2-*a*]pyrimidin-2,4(3*H*)dione (**15**).

A solution of 3.0 g. (0.027 mole) of 2-amino-3-methylpyridine in 10.0 g. (0.04 mole) of diethyl benzylmalonate was placed in an oil bath preheated to 155°. At 165° weak effervescence was noted: at 195° effervescence was vigorous, and within 10 minutes, the reaction mixture became solid. The total heating period at *ca.* 195° was 1 hour. The cooled reaction mixture was filtered with suction, the solid was washed with 5 ml. of acetonitrile, and air-dried to give 5.25 g. of crude product. Recrystallization from 75 ml. of *N,N*-dimethylformamide gave 3.20 g. (45% yield) of **15**, m.p. >250°.

Anal. Calcd. for $C_{16}H_{14}N_2O_2$: C, 72.17; H, 5.31; N, 10.52. Found: C, 71.93; H, 5.13; N, 10.66.

REFERENCES AND NOTES

(1) H. L. Yale, *J. Heterocyclic Chem.*, 12, 427 (1975).

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(3) H. L. Yale and E. R. Spitzmiller, *J. Heterocyclic Chem.*, 14, 241 (1977).

(4) *idem.*, *ibid.*, 14, 637 (1977).

(5) T. Kato and S. Masuda, *Chem. Pharm. Bull.*, **22**, 1542 (1974).

(6) A. J. Fatiada, *Synthesis*, 65 (1976).

(7) U. Jahn and G. Mixich, *Psychopharmacologia*, **46**, 191 (1976). See also, E. Wei and H. Loh, *Science*, **193**, 1262 (1976).

(8) Jahn and Mixich (*vide supra*) have shown that the "wet-dog shakes syndrome" was antagonized by narcotic analgesics, narcotic antagonists, psyco-sedative drugs as yohimbine, cocaine, D,L-amphetamine and apomorphine, while non-narcotic analgesics as physostigmine, atropine, L-dopa, and a variety of ganglionic, adrenergic, serotonin and histamine antagonists do not block that syndrome. In view of these observations, compounds like **4** and **5** can be visualized from a practical point of view as: (a) diagnostic agents for morphine addition, (b) as screens to differentiate the potential of a compound for producing dependence, and (c) as a differential screen for pharmacodynamic activity. It is of interest, also, that E. Wei and H. Loh, *Science*, **193**, 1262 (1976) have shown that the endogenous peptides, methionine-enkephalin and β-endorphin, with activities similar to those of morphine, also induced addiction in rats, and when those treated animals were challenged, they also developed the "wet-dog shakes syndrome."