REACTION OF METHYL 2-BENZOYLAMINO-3-DIMETHYLAMINOPROPENOATE WITH HETEROCYCLIC HYDROXY COMPOUNDS. THE SYNTHESIS OF FUSED PYRANOAZINES

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Abstract - Methyl 2-benzoylamino-3-dimethylaminopropenoate(1)reacts in acetic acid with monocyclic or bicyclic heterocyclic compounds with two hydroxy or potential hydroxy groups in 1,3-position to give fused pyranones. Accordingly, derivatives of 2*H*-pyrano[3,2-*c*]pyridine(3), 2*H*-pyrano[3,2-*c*]quinoline (9,10,and 11), 2*H*-pyrano[2,3-*d*]-pyridazine (13), 8*H*-pyrano[3,2-*d*]tetrazolo[1,5-*b*]pyridazine (16), pyrano[4,3-*b*]pyran (18), and 2*H*-pyrano[2,3-*c*]-pyridine (22) were obtained.

Recently, methyl 2-benzoylamino-3-dimethylaminopropenoate (1)[1,2] has been used as a versatile reagent in the synthesis of heterocyclic systems in which the α-amino acid structural element is incorporated in the cyclic system. In this connection, heterocyclic amines with an amino group at α-position in respect to ring nitrogen atom have been transformed into fused azinopyrimidones,[3] while aromatic and heteroaromatic hydroxy compounds with an active or potentially active methylene group, such as resorcinol, monohydroxy- or dihydroxynaphthalenes, barbiturates and pyranones afford the corresponding benzopyranones,[4] isomeric naphthopyranones and

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Dedicated to Professor E. C. Taylor, Princeton University, on occasion of his 70th birthday.

naphthodipyranones,[5-7] pyrazolopyranones and pyranopyrimidines.[4,8]

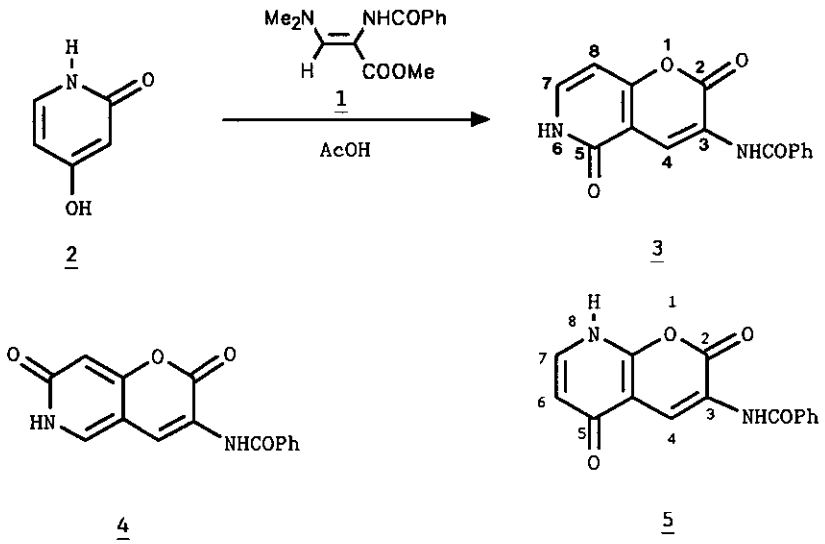
In this paper we report on the further application of the reaction of methyl 2-benzoylamino-3-dimethylaminopropenoate (1) with some heterocyclic systems with one or two hydroxy or potential hydroxy groups to form fused pyranones.

4-Hydroxypyridin-2(1*H*)-one (2) reacts with 1 to give a derivative of a bicyclic system. Since the reagent can nucleophilically attack either the position 3 or 5, followed by cyclization, in which either of the two hydroxy or potential hydroxy groups is involved, three isomeric systems (3), (4) or (5) can be formed.

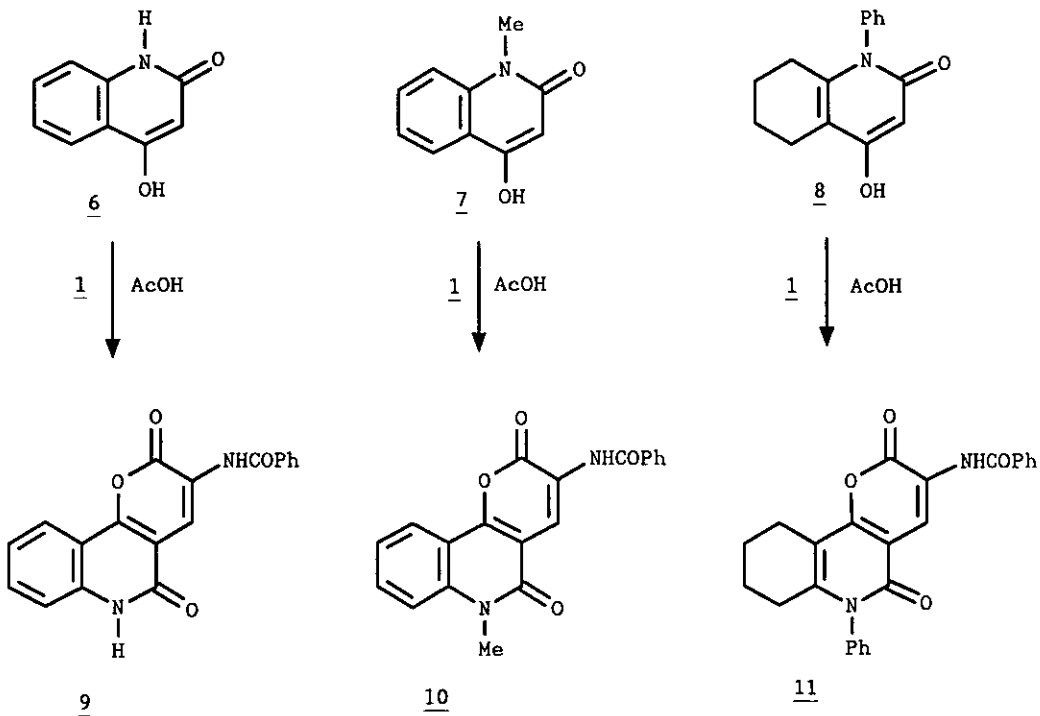
Since the coupling constant is significant for two adjacent protons, the structure (4) is eliminated. The primary reaction therefore starts at position 3, followed by cyclization to hydroxy group either at position 4 to give (3) or at position 2 to give (5). The magnitude of the coupling constant, $J_{7,8}$ = 7.8 Hz, strongly suggests the structure (3). For the isomeric system (5), one would expect much smaller coupling constant, $J_{6,7}$ = 4-5 Hz, by comparison of various fused pyridine systems.[9] (Scheme 1).

In quinoline series, 4-hydroxyquinolin-2(1*H*)-one (6), 1-methyl- (7) and 1-phenyl-5,6,7,8-tetrahydro (8) derivatives were selected. They afforded with 1 in acetic acid the corresponding 3-benzoylamino-2*H*-pyrano[3,2-*c*]-quinoline-2,5-dione derivatives (9), (10), and (11), respectively. Some other hydroxypyridine and hydroxyquinoline derivatives, such as 3-hydroxypyridin-2(1*H*)-one, 3-hydroxy-6-methyl-2-nitropyridine, 4-methylquinolin-2(1*H*)-one, quinolin-4(1*H*)-one, 5-hydroxyquinoline, 5-hydroxyisoquinoline, and 8-hydroxyquinoline and its 1-oxide do not react under the same reaction conditions. (Scheme 2).

In pyridazine and fused pyridazine series we found that 5-hydroxy-6-phenylpyridazin-3(2*H*)-one (12) and 7-hydroxy-6-phenyltetrazolo[1,5-*b*]pyri-



Scheme 1

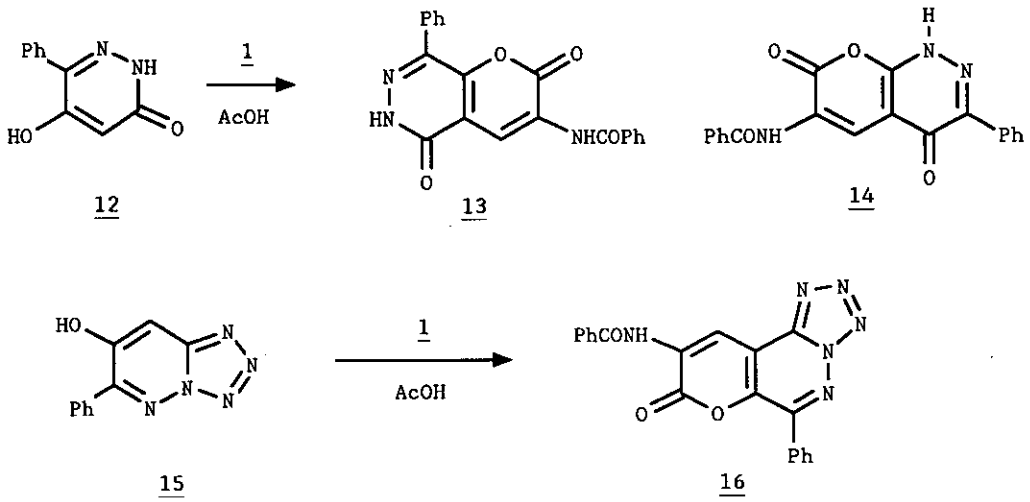


Scheme 2

dazine (15) gave with 1 in acetic acid the corresponding 3-benzoylamino-8-phenyl-5,6-dihydro-2*H*-pyrano[2,3-*d*]pyridazine-2,5-dione (13) and 9-benzoylamino-6-phenylpyrano[3,2-*d*]tetrazolo[1,5-*b*]pyridazin-8-on (16), while 6-chloro-2-phenylpyridazin-3(2*H*)-one, 2-methyl-6-phenyl-4,5-dihydropyridazin-3(2*H*)-one, 8-hydroxy-6-methyl-*s*-triazolo[4,3-*b*]pyridazine and 6-hydroxy-3-phenyl-*s*-triazolo[4,3-*b*]pyridazine do not react under these conditions. (Scheme 3).

In pyranone series, triacetic acid lactone (17) reacted with 1 in acetic acid to give 3-benzoylamino-7-methyl-2*H*,5*H*-pyrano[4,3-*b*]pyran-2,5-dione (18), which has been obtained previously from 17 and 4-ethoxymethylene-2-phenyl-4,5-dihydro-1,3-oxazol-5-one (19).[10] In the case of butyl 2,2-dimethyl-3,4-dihydro-4-oxo-2*H*-pyran-6-carboxylate (20) one would expect to obtain the bicyclic system (21).

However, the structure of the isolated product turned out to be methyl 2,2-dimethyl-3,4,7,8-tetrahydro-4,8-dioxo-2*H*-pyrano[2,3-*c*]pyridine-6-carboxylate (22). This structure is supported by the following observations. The elemental analysis shows that the molecular formula is $C_{12}H_{13}NO_5$ with the molecular peak, M^+ = 251, in the mass spectrum. In ^1H nmr spectrum there are a singlet at δ = 1.58 ppm, integrating for six protons corresponding to two equivalent methyl groups, a singlet at δ = 2.77 ppm integrating for two protons corresponding to CH_2 group, a singlet at δ = 3.94 ppm integrating for three protons corresponding to methoxy group, a singlet in aromatic region at δ = 7.41 ppm, integrating for one proton corresponding to H_5, and a broad exchangable singlet at δ = 9.80 ppm corresponding to NH group. There are no signals corresponding to butyl ester group and phenyl group. The compound (22) was further transformed with hydrazine hydrate in ethanol into hydrazonohydrazide (23). (Scheme 4).



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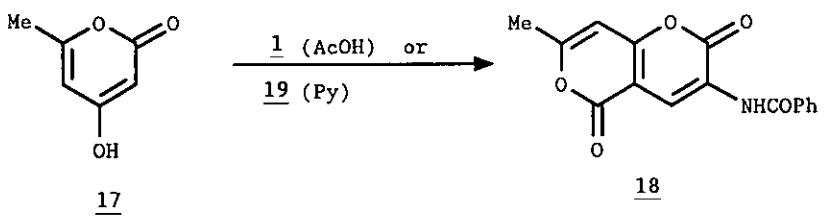
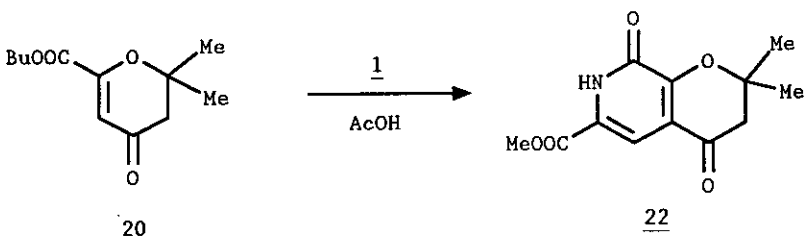
15 16

Scheme 3



17 18



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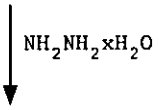

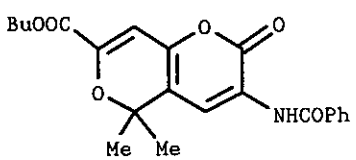

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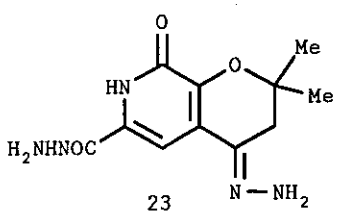

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Scheme 4

EXPERIMENTAL

Melting points were taken on a Kofler micro hot stage. ^{1}H Nmr spectra were recorded on a Varian EM 360 L spectrometer with TMS as internal standard, and elemental analyses for C, H, and N on a PERKIN-ELMER CHN Analyser 2400. The following compounds were prepared according to the procedure reported in the literature: 4-hydroxyquinolin-2(1*H*)-one (6),[11] 4-hydroxy-1-phenyl-5,6,7,8-tetrahydroquinolin-2(1*H*)-one (8),[12] 4-hydroxy-6-phenylpyridazin-3(2*H*)-one (12),[13] 7-hydroxy-6-phenyltetrazolo[1,5-*b*]pyridazine (15),[14] 6-chloro-2-phenylpyridazin-3(2*H*)-one,[13] 8-hydroxy-6-methyl-*s*-triazolo[4,3-*b*]-pyridazine,[15] and 6-hydroxy-3-phenyl-*s*-triazolo[4,3-*b*]pyridazine.[16]

3-Benzoylamino-5,6-dihydro-2*H*-pyrano[3,2-*c*]pyridine-2,5-dione (3). - A suspension of 4-hydroxypyridin-2(1*H*)-one (2) (333 mg, 0.003 mol) and 1 (744 mg, 0.003 mol) in acetic acid (5 ml) was heated under reflux (20 min). The solid was, after cooling to room temperature, collected by filtration and washed with ethanol (3 ml) to give 3 (161 mg, 57 %), mp 320°C (from DMF), nmr(DMSO-d_6) δ: 6.36 (1H, d, J = 7.8 Hz, H_7), 7.40-7.63 (4H, m, PhCO, H_8), 7.80-8.05 (2H, m, PHCONH), 8.53 (1H, s, H_4), 9.60 (1H, br s, CONH), 11.90 (1H, br s, NH). Anal. Calcd for $C_{15}H_{10}N_2O_4$: C, 63.83; H, 3.57; N, 9.93. Found: C, 63.67; H, 3.65; N, 9.89.

In the same manner the following compounds were prepared:

3-Benzoylamino-5,6-dihydro-2*H*-pyrano[3,2-*c*]quinoline-2,5-dione (9). - This compound was prepared from 4-hydroxyquinoline-2(1*H*)-one (6) and 1 in 72 % yield, mp > 320°C (from DMF), nmr (DMSO-d_6) δ: 7.20-8.20 (9H, m, PhCO, H_7, H_8, H_9, H_{10}), 8.78 (1H, s, H_4), 9.80 (1H, br s, CONH), 12.00 (1H, br s, NH). Anal. Calcd for $C_{19}H_{12}N_2O_4$: C, 68.67; H, 3.64; N, 8.43. Found: C, 68.77; H, 3.56; N, 8.61.

3-Benzoylamino-6-methyl-5,6-dihydro-2*H*-pyrano[3,2-*c*]quinoline-2,5-dione (10). This compound was prepared from 4-hydroxy-1-methylquinolin-2(1*H*)-one (7) and 1 in 77 % yield, mp 261-262°C (from DMF), nmr (DMSO-d_6) δ: 3.71 (3H, s, 6-Me), 7.30-8.20 (9H, m, PhCO, H_7, H_8, H_9, H_{10}), 8.77 (1H, s, H_4), 9.75 (1H, br s, CONH). Anal. Calcd for $C_{20}H_{14}N_2O_4$: C, 69.39; H, 4.07; N, 8.09. Found: C, 68.92; H, 4.09; N, 8.01.

3-Benzoylamino-6-phenyl-5,6,7,8,9,10-hexahydro-2*H*-pyrano[3,2-*c*]quinoline-2,5-dione (11). - This compound was prepared from 4-hydroxy-1-phenyl-5,6,7,8-tetrahydroquinoline-2(1*H*)-one (8) (241 mg, 0.001 mol) and 1 (248 mg, 0.001 mol) in 57 % yield, mp 300-302°C (from DMF), nmr (DMSO-d_6) δ: 1.67 (4H, m, 8-CH_2, 9-CH_2), 2.13 (2H, m, 10-CH_2), 2.60 (2H, m, 7-CH_2), 7.20-7.73 (8H, m, NPh, COPh), 7.90-8.13 (2H, m, COPh), 8.63 (1H, s, N_4), 9.78 (1H, br s, CONH). Anal. Calcd for $C_{25}H_{20}N_2O_4$: C, 72.80; H, 4.89; N, 6.79. Found: C, 73.03; H, 4.88; N, 6.78.

3-Benzoylamino-8-phenyl-5,6-dihydro-2*H*-pyrano[2,3-*d*]pyridazine-2,5-dione (13). This compound was prepared from 4-hydroxy-6-phenylpyridazin-3(2*H*)-one (12) (188 mg, 0.001 mol) and 1 (248 mg, 0.001 mol) in 28 % yield, mp 320°C (from a mixture of ethanol and DMF), nmr (DMSO-d_6) δ: 7.47-8.12 (10H, m, COPh, 8-Ph), 8.71 (1H, s, H_4). Anal. Calcd for $C_{20}H_{13}N_3O_4$: C, 66.85; H, 3.65; N, 11.70. Found: C, 66.61; H, 3.67; N, 11.45.

3-Benzoylamino-6-phenyl-8*H*-pyrano[3,2-*d*]tetrazolo[1,5-*b*]pyridazin-8-one (16). This compound was prepared from 7-hydroxy-6-phenyltetrazolo[1,5-*b*]pyridazine (15) (426 mg, 0.002 mol) and 1 (496 mg, 0.002 mol) in 20 % yield, mp 250°C (decomp.), nmr (DMSO-d_6) δ: 7.40-8.15 (10H, m, 6-Ph, COPh), 9.12 (1H, s, H_{10}), 10.40 (1H, br s, CONH). Anal. Calcd for $C_{20}H_{12}N_6O_3$: C, 62.50; H , 3.15; N, 21.87. Found: C, 62.24; H, 3.45; N, 21.61.

3-Benzoylamino-7-methyl-2*H*,5*H*-pyrano[4,3-*b*]pyran-2,5-dione (18). - This compound was prepared from triacetyl lactone (17) (225 mg, 0.002 mol) and 1 (496 mg, 0.002 mol) in 82 % yield, mp 261-263°C (from a mixture of ethanol - DMF), nmr ($CDCl_3$) δ : 2.40 (3H, s, 7-Me), 6.27 (1H, s, H_8), 7.53-7.77 (3H, m, COPh), 7.89-8.17 (2H, m, COPh), 8.70 (1H, br s, CONH), 9.03 (1H, s, H_4). Anal. Calcd for $C_{16}H_{11}NO_5$: C, 64.65; H, 3.73; N, 4.71. Found: C, 64.81; H, 3.59; N, 4.41.

Methyl 2,2-dimethyl-4,8-dioxo-3,4,7.8-tetrahydro-2*H*-pyrano[2,3-*c*]pyridine-6-carboxylate (22). - This compound was prepared from butyl 2,2-dimethyl-3,4-dihydro-4-oxo-2*H*-pyran-6-carboxylate (20) (2.51 g, 0.01 mol) and 1 (2.48 g, 0.01 mol) in 21 % yield, mp 226-228°C (from ethanol), nmr ($CDCl_3$) δ: 1.58 (6H, s, 2,2-diMe), 2.77 (2H, s, 3-CH_2), 3.94 (3H, s, COOMe), 7.41 (1H, s, H_5), 9.80 (1H, br s, NH). Anal. Calcd for $C_{12}H_{13}NO_5$: C, 57.37: H, 5.22; N, 5.58. Found: C, 57.62; H, 5.12; N, 5.40.

2,2-Dimethyl-4-hydrazono-8-oxo-3,4,7,8-tetrahydro-2*H*-pyrano[2,3-*c*]pyridine-6-carbohydrazide (23). - A solution of 22 (180 mg, 0.00072 mol) hydrazine hydrate (80 % aqueous solution, 2 ml, 0.03 mol) in ethanol (20 ml) was heated under reflux (2 h). The solution was evaporated to one-half in vacuo and the residue was, after cooling to room temperature, collected by filtration to give 23 in 63 % yield, mp 268°C ethanol - DMF), nmr (DMSO-d_6) δ: 1.30 (6H, s, 2,2-diMe), 2.53 (2H, s, 3-CH_2), 5.80 (2H, br s), 6.90 (6H, br s) (NH, NH_2, $NHNH_2$), 7.26 (1H, s, H_5). Anal. Calcd for $C_{11}H_{15}N_5O_3$: C, 49.80; H, 5.70; N, 26.40. Found: C, 49.97; H, 5.68; N, 26.10.

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