

A CONVENIENT SYNTHESIS OF ETHYL- β -DIOXOHYDROPYRIDINYL,
ETHYL- β -DIHYDRODIOXOPYRIDO[3,2-c]PYRIDAZINYL AND ETHYL-
 β -OXOPYRANYLACRYLATE DERIVATIVES

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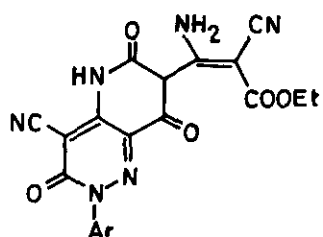
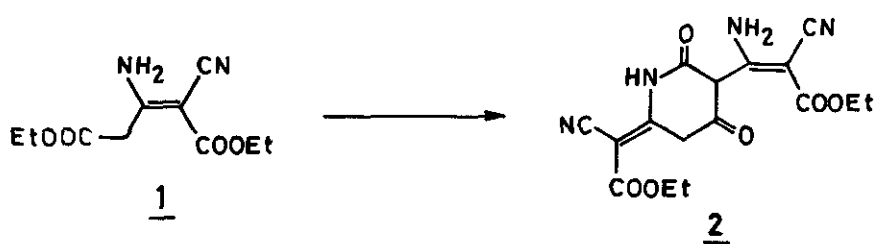
Abstract- A variety of pyridine, pyrido[3,2-c]pyridazine and pyran derivatives was synthesized from the enamino-nitrile derivative diethyl 3-amino-2-cyano-2-pentenedioate (1) as a starting material.

Polyfunctional nitriles are highly reactive reagents that have been extensively used in heterocyclic synthesis¹⁻³. In the course of our investigations on the reactions of activated nitriles⁴⁻⁷ for developing simple, new and efficient procedures for the synthesis of heterocycles, we report here a new synthesis of polyfunctional pyridine, pyrido[3,2-c]pyridazine and pyran derivatives starting with diethyl 3-amino-2-cyano-2-pentenedioate (1)⁸.

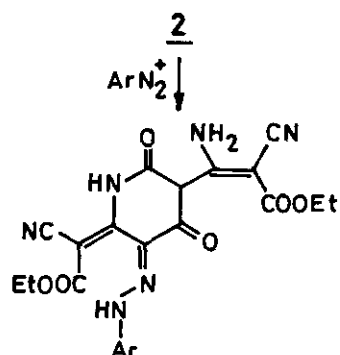
Thus boiling of 1 (0.01 mole) in pyridine (50 ml) for 4 h (TLC monitoring) yielded a mixture of products which is separated by column chromatography on silica gel using ethyl acetate / methanol (19/1) as an eluent to give a major colourless product (56% yield) of molecular formula $C_{16}H_{16}N_4O_6$ ($M^+ = 360$) together with three other fractions. The structure of the major product could be formulated as 2 based on elemental analysis and spectral data. Structure 2 is corresponding to condensation of two molecules of 1 with elimination of two molecules of ethanol. Trials to identify the three other fractions were unsuccessful.

Coupling of 2 (0.01 mole) with arene diazonium chlorides afforded 3a-c which were readily cyclised on refluxing (2 h) in acetic acid (30 ml) - hydrochloric acid (2 ml) mixture via ethanol elimination to the pyrido[3,2-c]pyridazine derivatives 4a-c.

Condensation of the hydrazide 5 (0.01 mole) which is readily obtained⁹ from 2 with an equimolar amount of acetylacetone in refluxing ethanol (30 ml) for 3 h in the presence of a catalytic amount of 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) (1 ml) afforded the oxopyran derivative 6 ($M^+ = 262$). The structure of 6 was based on elemental analysis and spectral data (cf. Tables 1 and 2). The formation of 6 is assumed to proceed via the sequence demonstrated in Chart 1.



4 a, Ar = C₆H₅
 b, Ar = C₆H₄ CH₃-p
 c, Ar = C₆H₄ Br-p



3 a, Ar = C₆H₅
 b, Ar = C₆H₄ CH₃-p
 c, Ar = C₆H₄ Br-p

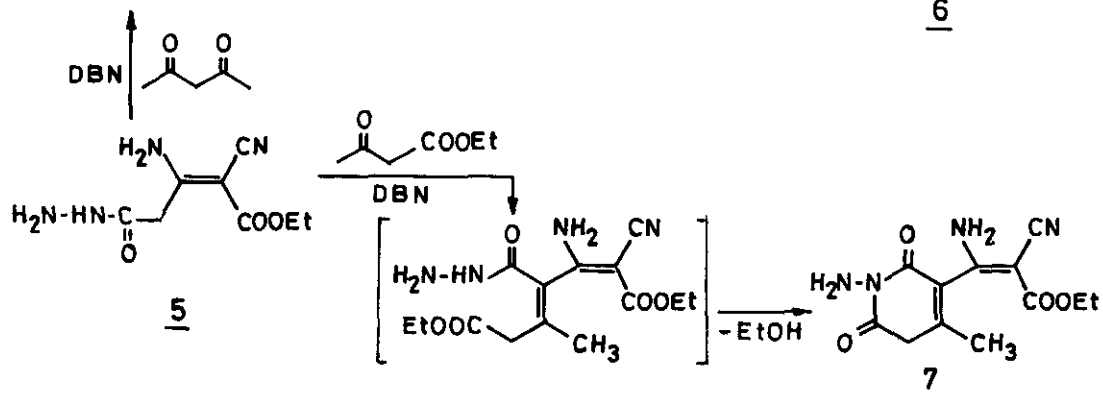
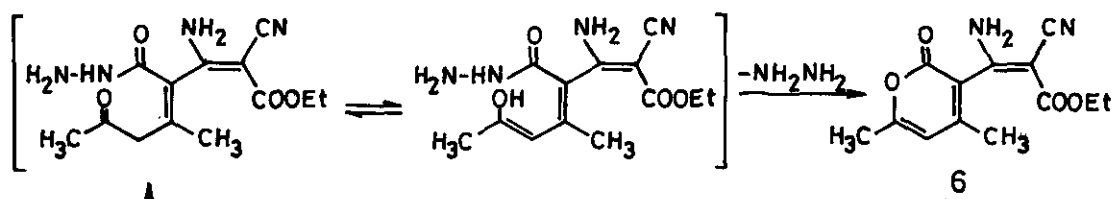


Chart 1

On the other hand, condensation of 5 (0.01 mole) with ethyl acetoacetate (0.01 mole) under similar conditions gave the pyridone derivative 7 ($M^+=278$) (cf. Chart 1).

The structures of the newly synthesized derivatives were established on the basis of analytical and spectroscopic data (Tables 1 and 2) and a variety of new heterocycles becomes now available. The biological activity of the products is now undertaken.

Table 1. List of the newly synthesized compounds.

Compound*	Mp. (°C)	Yield (%)	Mol. Formula	C % Calculated (Found)	H % Calculated (Found)	N % Calculated (Found)
<u>2</u>	179	56	$C_{16}H_{16}N_4O_6$	53.33 (53.20)	4.44 (4.20)	15.55 (15.70)
<u>3a</u>	241	75	$C_{22}H_{20}N_6O_6$	56.89 (57.10)	4.31 (4.30)	18.10 (18.20)
<u>3b</u>	202	80	$C_{23}H_{22}N_6O_6$	57.75 (57.80)	4.60 (4.50)	17.57 (17.30)
<u>3c</u>	189	72	$C_{22}H_{19}N_6O_6Br$	48.62 (48.80)	3.50 (3.40)	15.46 (15.50)
<u>4a</u>	196	85	$C_{20}H_{14}N_6O_5$	57.41 (57.30)	3.35 (3.40)	20.09 (20.10)
<u>4b</u>	300	79	$C_{21}H_{16}N_6O_5$	58.33 (58.40)	3.70 (3.60)	19.44 (19.60)
<u>4c</u>	207	81	$C_{20}H_{13}N_6O_5Br$	48.28 (48.30)	2.61 (2.70)	16.90 (16.80)
<u>6</u>	210	85	$C_{13}H_{14}N_2O_4$	59.54 (59.60)	5.34 (5.20)	10.68 (10.80)
<u>7</u>	257	68	$C_{12}H_{14}N_4O_4$	51.79 (51.90)	5.03 (5.10)	20.14 (20.30)

* All compounds are crystallized from ethanol except 3b, 6 and 7 which were crystallized from dioxan.

Table 2. Ir and ^1H nmr data of compounds 2, 3a, 4a, 6, and 7

Compound	Ir [cm^{-1}] Selected bands	^1H Nmr (δ ppm) [DMSO- d_6]
<u>2</u>	3395, 3380, 3320 (NH_2 and NH); 2225 2210 (two CN); 1760, 1750 (two ester CO); 1690, 1680 (ring CO); 1620 (C=N); 1600 (C=C).	1.3 (t, J=7 Hz, 6H, two ester CH_3); 1.5 (s, 3H, piperidone protons); 4.1 (q, J=7 Hz, 4H, two ester CH_2); 6.7 (s, 2H, NH_2); 8.5 (s, 1H, NH).
<u>3a</u>	3380 - 3250 (NH_2 and NH); 2220, 2200 two CN); 1765, 1750 (two ester CO); 1680, 1665 (ring CO); 1620 (C=N); 1600 (C=C).	1.3 (t, J=7 Hz, 6H, two ester CH_3); 1.4 (s, 1H, piperidone-H); 4.2 (q, J=7 Hz, 4H, two ester CH_2); 6.5 (s, 2H, NH_2); 7.3 - 8.1 (m, 7H, C_6H_5 and two NH).
<u>4a</u>	3450 - 3250 (NH_2 and NH); 2225 (CN); 1760 (ester CO); 1690, 1680, 1660 (ring CO); 1625 (C=N); 1610 (C=C).	1.1 (t, J=7 Hz, 3H, ester CH_3); 1.4 (s, 1H, piperidone-H); 4.1 (q, J=7 Hz, 2H, ester CH_2); 5.2 (s, 2H, NH_2); 7.2 - 7.8 (m, 6H, C_6H_5 and NH).
<u>6</u>	3400, 3300 (NH_2); 2210 (CN); 1770 (ester CO); 1695 (ring CO); 1620 (C=N); 1600 (C=C).	1.2 (t, J=7 Hz, 3H, ester CH_3); 2.4 (s, 3H, CH_3); 2.8 (s, 3H, CH_3); 4.2 (q, J=7 Hz, 2H, ester CH_2); 6.9 (s, 1H, pyran-H); 7.6 (s, 2H, NH_2).
<u>7</u>	3390 - 3300 (NH_2); 2210 (CN); 1770 (ester CO); 1680, 1670 (ring CO); 1625 (C=N); 1600 (C=C).	1.1 (t, J=7 Hz, 3H, ester CH_3); 1.4 (s, 2H, pyridone-H3); 2.7 (s, 3H, CH_3); 4.1 (q, J=7 Hz, 2H, ester CH_2); 5.4 (s, br, 4H, two NH_2).

ACKNOWLEDGEMENT F. M. Abdel Galil is deeply indebted to DAAD, Bonn/F.R.G. for granting a fellowship during summer 1987 and to Prof. Dr. W. Steglich, Institute of Organic Chemistry and Biochemistry, University of Bonn/F.R.G. for facilities that enabled spectral measurements.

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Received, 19th May, 1988