Chemistry of Heterocyclic Compounds, Vol. 31, No. 7, 1995

METHODS FOR THE SYNTHESIS OF 4-PYRAZOLYL- AND 4-PYRIDYL-5-OXO-1,4,5,7-TETRAHYDROFURO[3,4-b]PYRIDINES

A. Sausin'sh, B. Chekavichus, and G. Duburs

The most suitable method for the synthesis of 4-pyrazolyl- or 4-pyridyl-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridines uses 4-chloro- or 4-acetoxyacetoacetic esters in various versions of the Hantsch synthesis with closure of a lactone ring during the reaction. Some of the intermediate products (2-chloromethyl- and 2-acetoxymethyl-1,4-dihydropyridines) were isolated. Cyclization with the formation of lactones does not occur in N-substituted 1,4-dihydropyridines.

It is known that 4-aryl-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridines (VIa) promote the transport of calcium ions across cell membranes and exhibit cardiotonic activity [1-3]. Only isolated examples of their 4-heteryl analogs have been synthesized [4].

The aim of the present work was to study the possibilities of synthesizing 4-heteryl- and, more specifically, 4-pyrazolyl- and 4-pyridyl-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridines (VI). Earlier we studied the synthesis and properties of 4-pyrazolyl-3,5-dialkoxycarbonyl-1,4-dihydropyridines [5].

The methods involving the cyclization of 2,6-dimethyl-3,5-dialkoxycarbonyl-1,4-dihydropyridines (IVa) to the lactones (VIa) by means of the perbromide of pyridinium bromide [6] or N-bromosuccinimide (NBS) [7] are well known.

The action of N-bromosuccinimide on the dihydropyridine (IVd) gave the furopyridine (VId). However, certain other 4-pyrazolyl (IVb, f) and 4-pyrrolyl derivatives of 1,4-dihydropyridine give difficultly separable mixtures of products with N-bromosuccinimide. As a result this method is not entirely suitable for the synthesis of 4-heterylfuropyridines (VI). It was also not possible to realize the cyclization of dihydroindenopyridine (VIIIa) to the corresponding lactone with N-bromosuccinimide.

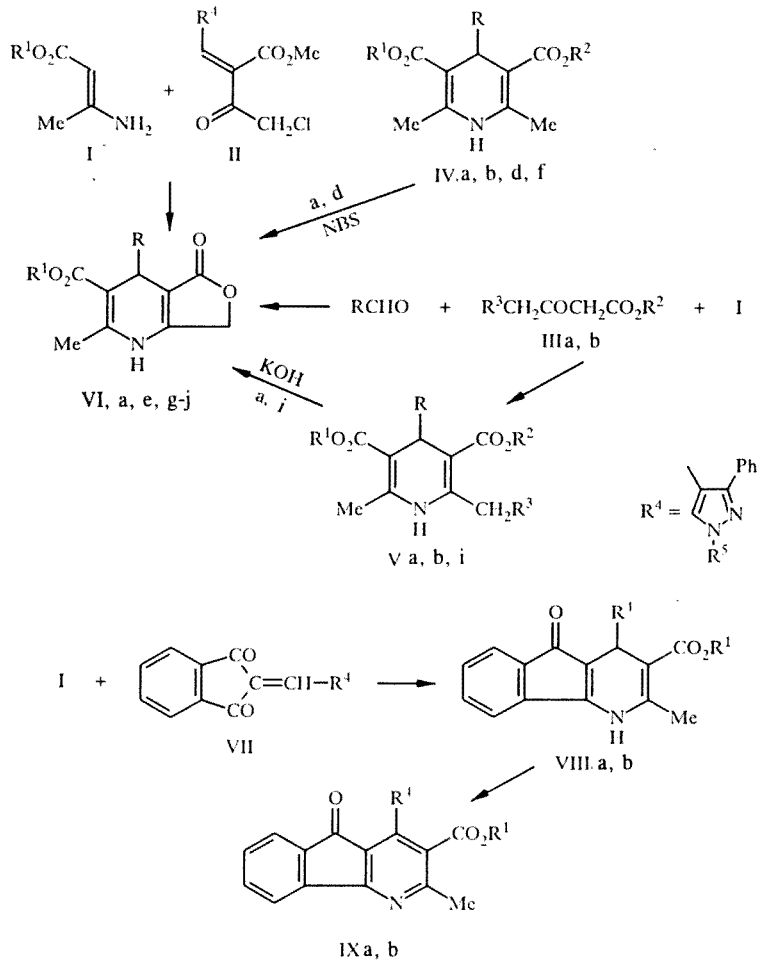
In the synthesis of compound (VIII) from 2-(pyrazolylmethylene)indane-1,3-dione (VII) and 3-aminocrotonic ester the expected dihydro compound (VIIIa) was only isolated in a small amount; the oxidized forms (IXa, b) were mainly formed, since the ylidene derivative (VII) can probably act as an oxidizing agent on the dihydropyridine during the reaction; such action has been demonstrated for 2-benzylidene-1,3-indanedione [8].

The method employing 4-chloro- or 4-acetoxyacetoacetic esters (III) in various versions of the Hantsch synthesis has been widely used in the synthesis of lactones (VIa). The obtained 2-chloromethyl- or 2-acetoxymethyl-1,4-dihydropyridines (Va) close the lactone ring after prolonged boiling or treatment with alkali [9, 10].

The two-component reaction between 2-(pyrazolylmethylene)-4-chloroacetoacetic ester (II) (a mixture of the E and Z isomers) and 3-aminocrotonic ester (I) with prolonged boiling leads not only to the Hantsch synthesis of dihydropyridine but also to closure of the lactone ring with the formation of the tetrahydrofuro[3,4-b]pyridine (VIc). The lactone (VI) is not formed in the three-component reaction between the aldehyde, 4-chloroacetoacetic ester (IIIa), and 3-aminocrotonic ester at room temperature; the intermediate 2-chloromethyl-1,4-dihydropyridine (Vb) was isolated. By using 4-acetoxyacetoacetic ester (IIIb) in this reaction with boiling in ethanol it was possible to isolate 2-acetoxymethyl-1,4-dihydropyridine (Vi), which undergoes cyclization to the lactone (VIi) under the influence of potassium hydroxide. It is more convenient to conduct the reaction without isolating the 2-acetoxy derivative (V); the tetrahydrofuropyridines (VIb, e, g, h, j) were obtained by adding a solution of potassium hydroxide to the reaction mixture.

Latvian Institute of Organic Synthesis, Riga. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, pp. 966-972, July, 1995. Original article submitted May 24, 1995.

0009-3122/95/3107-0841$12.50



II R^5 = C_6H_5; IIIa R^2 = CH_3, R^3 = Cl; IIIb R^2 = C_2H_5, R^3 = CH_3COO; IVa, Va, VIa R = aryl, R^1, R^2 = alkyl R^3 = Cl, CH_3COO; IVb, Vb, VIb R = R^4, R^1 = R^2 = CH_3, R^3 = Cl, R^5 = H; VIc R = R^4, R^1 = CH_3, R^5 = C_6H_5; IVd, VId R = R^4, R^1 = R^2 = C_2H_5, R^5 = C_6H_5; VIe R = R_4, R^1 *p*-C_3H_7, R^5 = H; IVf R = R^4, R^1 = R^2 = n-C_4H_9, R^5 = H; VIg R = R^4, R^1 = $CH_2CH=CH_2$, R^5 = H, VIh R = R^4, R^1 = *p*-$C_{14}H_{29}$, R^5 = H; V i, VI i R = 3- pyridyl, R^1 = CH_3, R^2 = C_2H_5, R^3 = CH_3COO; VI J R = 4- pyridyl, R^1 = CH_3; VII, VIII, IX R^5 = C_6H_5; VIIIa, IXa R^1 = CH_3; VIIIb, IXb R^2 = C_2H_5

Unlike the N-unsubstituted analogs the 3-arylaminocrotonic ester (X) gives 1-aryl-2-chloromethyl-1,4-dihydropyridine (XI) with the ester (II). The product is a stable substance and does not undergo cyclization to the lactone either after heating in solution for many hours or in the molten state. This agrees with our previously discovered reactivity of 2-bromomethyl-1,4-dihydropyridines [7], due to their steric strain. Stuart—Briegleb models show that rotation of the CH_2Br group (and also the CH_2Cl group) is impossible in 1-substituted 1,4-dihydropyridines. As a result the approach of the reaction centers for closure of the lactone ring is unlikely. The restricted rotation of the CH_2Cl group in compound (XI) is demonstrated in the PMR spectra by signals for the ethylene group at position 6 at 4.06 and 4.97 ppm in the form of an AB quartet.

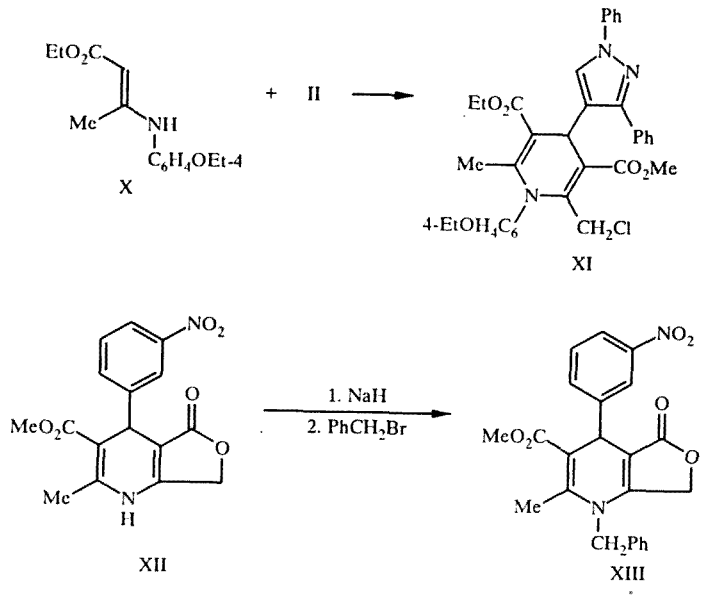
At the same time it is possible to obtain the N-substituted derivatives by the N-alkylation of 1,4,5,7-tetrahydrofuro[3,4-b]pyridines [11]. We realized this in the case of the N-benzylation of the lactone (XII).

Experiments conducted in the Laboratory of Pharmacology at the Latvian Institute of Organic Synthesis showed that 4-pyrazolyl- and 4-pyridylfuropyridines (VI) only have a slight effect on the cardiovascular system.

EXPERIMENTAL

The PMR spectra were recorded on a Bruker WH-90 instrument at 90 MHz in DMSO-d_6 solution with TMS as internal standard. The IR spectra were obtained on a Perkin-Elmer 580B spectrometer for suspensions in Nujol. The UV spectra were

obtained on a Carl Zeiss/Jena Specord M-40 spectrophotometer in ethanol. The mass spectrum was recorded on an AEI MS-50 instrument.



The reactions and the individuality of the synthesized compounds were monitored on Silufol UV-254 plates in the 9:7:1 chloroform–hexane–acetone and 20:1 benzene–ethyl acetate solvent systems.

The elemental analyses of the obtained compounds for C, H, N, and Cl correspond to the calculated data.

The characteristics of compounds (II, IV-IX, XI, XIII) are summarized in Tables 1 and 2.

Methyl 2-[(1′,3′-Diphenyl-4′-pyrazolyl)methylene]-4-chloroacetoacetate (II). A solution of 1.24 g (5 mmole) of 1,3-diphenyl-4-formylpyrazole, 1.5 g (5 mmole) of methyl 4-chloroacetoacetate, 0.06 ml of piperidine, and 0.04 ml of acetic acid in 50 ml of benzene was boiled for 4 h using a Dean—Stark tube. The product was evaporated under vacuum, rubbed with methanol, and crystallized from methanol.

3,5-Dialkoxycarbonyl-2,6-dimethyl-4-(3′-phenyl-4′-pyrazolyl)-1,4-dihydropyridines (IVb, f). A solution of 0.01 mole of 3-phenyl-4-formylpyrazole, 0.02 mole of acetoacetic ester, and 3 ml of 25% aqueous ammonia in 10 ml of ethanol was boiled for 7 h.

A. Compound (IVb). After cooling the precipitate was separated and crystallized from ethanol.

B. Compound (IVf). Part of the compound separated after cooling. The other part was obtained after evaporation of the filtrate under vacuum and treatment of the residue with ethyl acetate. The product was crystallized from a 1:1 mixture of ethanol and water.

3,5-Dimethoxycarbonyl-2-methyl-4-(3′-phenyl-4′-pyrazolyl)-6-chloromethyl-1,4-dihydropyridine (Vb). A solution of 0.86 g (5 mmole) of 3-phenyl-4-formylpyrazole, 0.75 g (5 mmole) of methyl 4-chloroacetoacetate, and 0.58 g (5 mmole) of methyl 3-aminocrotonate in 10 ml of isopropanol was stirred at room temperature for 20 h. The substance was isolated by the addition of 1 ml of water and crystallized from methanol.

6-Acetoxymethyl-2-methyl-3-methoxycarbonyl-4-(3′-pyridyl)-5-ethoxycarbonyl-1,4-dihydropyridine (Vi). A solution of 1.07 g (0.01 mole) of 3-pyridinecarbaldehyde, 1.15 g (0.01 mole) of methyl 3-aminocrotonate, and 1.88 g (0.01 mole) of ethyl 4-acetoxyacetoacetate in 10 ml of ethanol was boiled for 23 h. Part of the compound separated after cooling, and part was obtained after evaporation of the filtrate under vacuum and treatment of the remaining oil with ethyl acetate. The product was crystallized from a 1:1 mixture of ethanol and water.

3-Alkoxycarbonyl-2-methyl-4-pyrazolyl(pyridyl)-1,4,5,7-tetrahydrofuro[3,4-b]pyridines (VI). Lactone (VIc). A solution of 0.3 g (3 mmole) of methyl 3-aminocrotonate and 0.99 g (3 mmole) of methyl 2-[(1′,3′-diphenyl-4′-pyrazolyl)methylene]-4-chloroacetoacetate (II) in 10 ml of methanol was boiled for 10 h. The precipitate was isolated after cooling and crystallized from methanol.

TABLE 1. Characteristics of Compounds (II, IV-IX, XI, XIII)

Compound	Molecular formula	mp, °C	UV spectrum, λ_{max} (log ε)	IR spectrum, ν, cm^{-1}	Yield, %
II	$C_{21}H_{17}ClN_2O_3$	90...95		3370, 1756, 1740, 1725, 1700	80
IV *b*	$C_{20}H_{21}N_3O_4$	254...256	205 (4,41), 245 (4,41), 353 (3,90)	3258, 1697, 1678, 1642, 1623	48
IV f	$C_{26}H_{33}N_3O_4$	166...168	205 (4,41), 244 (4,43), 353 (3,92)	3257, 1704, 1667, 1637, 1618	41
V b	$C_{20}H_{20}ClN_3O_4$	180...181	360 (3,90)	3320, 3210, 3070, 1700, 1680	26
V i	$C_{19}H_{22}N_2O_6$	139...141			25
VI b	$C_{19}H_{17}N_3O_4$	228...230	208 (4,43), 237 (4,35), 337 (3,91)	3375, 3285, 1748, 1738 sh, 1733, 1699, 1685, 1672	28
VI c	$C_{25}H_{21}N_3O_4$	255...257		3340, 1740, 1698, 1675	63
VI d	$C_{26}H_{23}N_3O_4$	248...249		3240, 1732, 1700, 1695	68
VI e	$C_{21}H_{21}N_3O_4$	198...199	207 (4,31), 238 (4,19), 343 (3,73)	3250, 1736, 1702, 1672	38
VI g	$C_{21}H_{19}N_3O_4$	230...232	206 (4,38), 237 (4,26), 343 (3,82)	3230, 3130, 3090, 1748 sh, 1736, 1705, 1672	38
VI h	$C_{32}H_{43}N_3O_4$	179...182	206 (4,44), 247 (4,31), 342 (3,86)	3262, 3200, 3145, 3095, 1724, 1712, 1690, 1666	26
VI i	$C_{15}H_{14}N_2O_4$	220...222	205 (4,17), 225 (4,37), 260 (3,75), 342 (3,90)		27
VI j	$C_{15}H_{14}N_2O_4$	180...182	204 sh (4,01), 226 (4,30), 260 (3,53), 343 (3,76)	3260, 3162, 3060, 1762, 1748, 1704, 1678	17
VI j · HCl	$C_{15}H_{14}N_2O_4 \cdot HCl$	205...210	205 (4,06), 226 (4,33), 261 (3,58), 346 (3,76)	3220, 3125, 3105, 3090, 2567, 1755, 1747, 1710, 1693	
VII*	$C_{25}H_{16}N_2O_2$	235...237		1730, 1684, 1606, 1587	86
VIII a	$C_{30}H_{23}N_3O_3$	240...242	208 (4,61), 264 (4,58), 345 (3,70), 474 (3,44)	3250, 3180, 1645, 1590	27
IX b	$C_{31}H_{23}N_3O_3$	200...203	206 (4,79), 254 (4,73), 278 (3,68)	1725, 1590, 1560	85
XI	$C_{35}H_{34}ClN_3O_5$	161...164	348 (3,48)	1700, 1690, 1650	26
XIII	$C_{23}H_{20}N_2O_6$	184...188		1750, 1740, 1700, 1685	47

*M^+ 376.

TABLE 2. Data from the PMR Spectra of Compounds (II, IV-IX, XI, XIII)

Compound	Chemical shifts, δ, ppm
II*	3,58 and 3,77 (3H, s, CH_3), 4,73 and 4,86 (2H, s, CH_2), 7,04...7,68 (11H, m, arom.+ 5'-H), 8,33 and 8,51 (1H, s, =CH)
IVb	2,22 (6H, s, 2,6-CH_3), 3,15 (6H, s, OCH_3), 5,04 (1H, s, 4-H), 7,18...7,80 (6H, m, C_6H_5 + 5'-H), 8,80 (1H, bs, NH of pyridine), 12,57 (1H, bs, NH of pyrazole)
IVf	0,75 [6H, t, $(CH_2)_3CH_3$], 0,93...1,38 [8H, m, $CH_2(CH_2)_2CH_3$], 2,18 (6H, s, 2,6-CH_3), 3,35...4,02 (4H, m, OCH_2), 5,09 (1H, s, 4-H), 7,18...7,84 (6H, m, C_6H_5 + 5'-H), 8,77 (1H, bs, NH of pyridine), 12,53 (1H, bs, NH of pyrazole)
Vb	2,17 (3H, s, 2-CH_3), 3,13 (3H, s, OCH_3), 4,64 (2H, s, CH_2), 5,04 (1H, s, 4-H), 7,17...7,71 (6H, m, C_6H_5 + 5'-H), 9,13 (1H, s, NH of pyridine), 12,55 (1H, bs, NH sextet,)
Vi*	1,22 (3H, t, $CH_2\underline{CH_3}$), 2,15 (3H, s, CH_3CO), 2,35 (3H, s, 2-CH_3), 3,62 (3H, s, OCH_3), 4,10 (2H, q, $\underline{CH_2}CH_3$), 4,99 (1H, s, 4-H), 5,30 (2H, s, CH_2O), 6,80 (1H, bs, NH), 7,12 (1H, dd, 5'-H), 7,55 (1H, dt, 4'-H), 8,35 (1H, dd, 6'-H), 8,49 (1H, d, 2'-H)
VIb	2,10 (3H, s, 2-CH_3), 2,99 (3H, s, OCH_3), 4,64 (2H, s, CH_2), 4,69 (1H, s, 4-H), 7,18...7,68 (6H, m, C_6H_5 + 5'-H), 9,51 (1H, bs, NH of pyridine), 12,55 (1H, bs, s, NH sextet)
VIc	2,20 (3H, s, 2-CH_3), 3,08 (3H, s, OCH_3), 4,79 (2H, s, CH_2), 4,82 (1H, s, 4-H), 7,11...7,88 (10H, m, C_6H_5), 8,20 (1H, s, 5'-H), 9,64 (1H, bs, NH)
VId	0,66 (3H, t, $CH_2\underline{CH_3}$), 2,17 (3H, s, 2-CH_3), 3,62 (2H, m, $\underline{CH_2}CH_3$), 4,71 (2H, s, CH_2 of lactone), 4,88 (1H, s, 4-H), 7,11...7,91 (10H, m, C_6H_5), 8,17 (1H, s, 5'-H), 9,62 (1H, bs, NH)
VIe	0,52 (3H, t, $CH_2\underline{CH_3}$), 0,99 (2H, sextet, $\underline{CH_2}CH_3$), 2,21 (3H, s, 2-CH_3), 3,42...3,89 (2H, m, $O\underline{CH_2}CH_2$), 4,77 (2H, s, CH_2 of lactone), 4,84 (1H, s, 4-H), 7,31...7,89 (6H, m, C_6H_5 + 5'-H), 9,68 (1H, bs, NH of pyridine), 12,71 (1H, bs, NH of pyrazole)
VIg	2,10 (3H, s, 2-CH_3), 4,03 (2H, m, OCH_2), 4,66 (2H, s, CH_2 of lactone), 4,73 (1H, s, 4-H), 4,83 (2H, m, $=CH_2$), 5,30 (1H, m, =CH), 7,16...7,69 (6H, m, C_6H_5 + 5'-H), 9,58 (1H, bs, NH of pyrazole) 12,57 (1H, bs, NH sextet)
VIh	0,70...1,30 [27H, m, $(CH_2)_{12}CH_3$], 2,14 (3H, s, 2-CH_3), 3,30...3,77 (2H, m, $O\underline{CH_2}CH_2$), 4,70 (2H, s, CH_2 of lactone), 4,78 (1H, s, 4-H), 7,21...7,78 (6H, m, C_6H_5 + 5'-H), 9,58 (1H, bs, NH of pyridine), 2,55 (1H, bs, NH of pyrazole)
VIi	2,27 (3H, s, 2-CH_3), 3,41 (3H, s, OCH_3), 4,67 (1H, s, 4-H), 4,79 (2H, s, CH_2), 7,19 (1H, dd, 5'-H), 7,47 (1H, dt, 4'-H), 8,22...8,38 (2H, m, 2'-H + 6'-H), 9,78 (1H, bs, NH)
VIj	2,28 (3H, s, 2-CH_3), 3,41 (3H, s, OCH_3), 4,67 (1H, s, 4-H), 4,78 (2H, s, CH_2), 7,12 (2H, dd, 3'-H + 5'-H), 8,38 (2H, dd, 2'-H + 6'-H), 9,83 (1H, s, NH)
VIj · HCl	2,34 (3H, s, 2-CH_3), 3,41 (3H, s, OCH_3), 4,82 (2H, s, CH_2), 4,97 (1H, s, 4-H), 6,03 (1H, bs, NH), 7,82 (2H, d, 3'-H + 5'-H), 8,77 (2H, d, 2'-H + 6'-H), 10,58 (1H, d, NH)
VII	7,42...8,06 (15H, m, arom. + 5'-H), 9,95 (1H, s, =CH)
VIIIa*	2,33 (3H, s, 2-CH_3), 3,31 (3H, s, OCH_3), 5,13 (1H, s, 4-H), 6,31 (1H, bs, NH), 7,17...7,91 (15H, m, arom.+ 5'-H)
IXb	0,88 (3H, t, $CH_2\underline{CH_3}$), 2,60 (3H, s, 2-CH_3), 4,00 (2H, q, $\underline{CH_2}CH_3$), 7,13...8,17 (14H, m, arom), 8,57 (1H, s, 5'-H)
XI*	1,13 (3H, t, $CH_2\underline{CH_3}$), 1,44 (3H, t, CH_2CH_3), 2,06 (3H, s, 2-CH_3), 3,26 (3H, s, OCH_3), 4,06 (5H, m, $\underline{CH_2}CH_3$ + CH_2Cl), 4,97 (1H, d, CH_2Cl), 5,44 (1H, s, 4-H), 6,84...7,93 (15H, m, arom.+ 5'-H)
XIII	2,28 (3H, s, 2-CH_3), 3,42 (3H, s, OCH_3), 4,73...5,00 (5H, m, 4-H + N—CH_2 + CH_2 of lactone), 7,08...8,15 (9H, m, arom.)

*The spectrum was recorded in deuterochloroform.

Lactone (VId). A solution of 0.47 g (0.01 mole) of dihydropyridine (IVd) [5] and 0.18 g (0.01 mole) of N-bromosuccinimide in 10 ml of chloroform was boiled for 1 h. The product was evaporated under vacuum, the oil was rubbed with ethanol, and the product was crystallized from ethanol.

Lactone (VIi). A 0.95-g sample of 6-acetoxymethyl-1,4-dihydropyridine (Vi) was dissolved in 5 ml of ethanol. A solution of 0.15 g of potassium hydroxide in 2 ml of ethanol was added, and the mixture was boiled for 30 min. Part of the substance separated after cooling, and part was precipitated by the addition of water. The product was crystallized from a 2:1 mixture of ethanol and water.

Lactones (VIb, e, g, h, j). A solution of 0.01 mole of the aldehyde, 0.01 mole of 3-aminocrotonic ester, and 0.01 mole of ethyl 4-acetoxyacetoacetate in 10 ml of ethanol was boiled for 20-25 h, and 0.56 g (0.01 mole) of potassium hydroxide

in 2 ml of ethanol was then added. The mixture was boiled for a further 30 min. The 4-pyrazolylfuropyridines (VIb, e, g, h) were isolated from the reaction mixture after cooling. Compounds (VIb, h) were crystallized from methanol, and compounds (VIe, g) from ethanol. 4-Pyridylfuropyridine (VIj) was precipitated by the addition of water to the reaction mixture and was crystallized from ethanol. The hydrochloride of the lactone (VIj) was obtained by the addition of a solution of hydrogen chloride in dry ether to a solution of the base (VIj) in absolute ethanol, and the product was crystallized from ethanol.

2-[(1′,3′-Diphenyl-4′-pyrazolyl)methylene]indane-1,3-dione (VII). A solution of 1.46 g (0.01 mole) of 1,3-indanedione, 2.48 g (0.01 mole) of 1,3-diphenyl-4-formylpyrazole, 0.12 ml of piperidine, and 0.08 ml of acetic acid in 100 ml of benzene was boiled for 30 min using a Dean—Stark tube. The product was evaporated under vacuum, rubbed with 100 ml of ethanol, and crystallized from acetic acid.

4-(1′,3′-Diphenyl-4′-pyrazolyl)-2-methyl-3-methoxycarbonyl-5-oxo-1,4-dihydroindeno[1,2-b]pyridine (VIIIa). A solution of 1.88 g (5 mmole) of 2-(pyrazolylmethylene)-1,3-indanedione (VII) and 0.57 g (5 mmole) of methyl 3-aminocrotonate in a solution of 30 ml of DMFA and 10 ml of acetic acid was heated at 100°C for 1 h. The solution was cooled, and the red crystals were filtered off. The product was a mixture of the dihydropyridine (VIIIa) and its oxidized form (IXa). The mixture was chromatographed on 220 × 260-mm plates with a 2-3-mm unfixed layer of silica gel L100/160 μ in the 20:1 benzene—ethyl acetate system, and the red band was collected. The product was eluted with acetone, the solvent was evaporated under vacuum, and the residue was crystallized from methanol.

4-(1′,3′-Diphenyl-4′-pyrazolyl)-2-methyl-5-oxo-3-ethoxycarbonylindeno[1,2-b]pyridine (IXb). A solution of 1.88 g (5 mmole) of 2-(pyrazolylmethylene)-1,3-indanedione (VII) and 0.64 g (5 mmole) of ethyl 3-aminocrotonate in 30 ml of acetic acid was boiled for 30 min. The solution was cooled, and the yellow crystals were filtered off. The product was crystallized from a 4:1 mixture of acetic acid and ethanol.

4-(1′,3′-Diphenyl-4′-pyrazolyl)-2-methyl-5-methoxycarbonyl-6-chloromethyl-3-ethoxycarbonyl-1-(4″-ethoxyphenyl)-1,4-dihydropyridine (XI). A solution of 0.95 g (2.5 mmole) of methyl 2-[(1′,3′-diphenyl-4′-pyrazolyl)methylene]-4-chloroacetoacetate (II) and 0.64 g (2.5 mmole) of ethyl 3-(4′-ethoxyphenylamino)crotonate (X) was boiled in 10 ml of methanol for 20 min. The precipitate separated after holding in the refrigerator (for several days). The product was crystallized from methanol.

1-Benzyl-2-methyl-3-methoxycarbonyl-4-(3′-nitrophenyl)-5-oxo-1,4,5,7-tetrahydrofuro[3,4-b]pyridine (XIII). A 0.6-g sample (2 mmole) of the lactone (XII) was dissolved in 10 ml of anhydrous dimethoxyethane. At room temperature 0.15 g (6 mmole) of sodium hydride was added. After 30 min, 0.62 g (4 mmole) of benzylbromide was added. The mixture was then boiled for 5 h and evaporated under vacuum. The oil was rubbed with water, and the product was crystallized from methanol.

REFERENCES

1. A. M. Brown, D. L. Kunze, and A. Yatani, Nature (London), No. 311, 570 (1984).
2. I. P. Skrastin'sh, V. V. Kastron, R. O. Vitolin', G. Ya. Dubur, M. S. Styvrinya, and K. A. Kaidaka, Khim.-farm. Zh., **23**, 1323 (1989).
3. L. Patmore, G. P. Duncan, B. Clarke, and A. J. Anderson, Br. J. Pharmacol., **99**, 687 (1990).
4. G. Frankowiak, H. Boeshagen, F. Bossert, S. Goldmann, H. Meyer, E. Wehinger, J. Stoltefuss, M. Schramm, G. Thomas, and R. Towart, Offenleg. 3,206,671 BRD; Chem. Abs., **98**, 215488 (1983).
5. B. S. Chekavichus, A. G. Odynets, A. É. Sausin'sh, D. A. Berzinya, R. M. Zolotoyabko, É. É. Liepin'sh, and G. Ya. Dubur, Khim.-farm. Zh., **21**, 959 (1987).
6. S. D. Young, Synthesis, No. 7, 617 (1984).
7. I. P. Skrastin'sh, V. V. Kastron, B. S. Chekavichus, A. É. Sausin'sh, R. M. Zolotoyabko, and G. Ya. Dubur, Khim. Geterotsikl. Soedin., No. 9, 1230 (1991).
8. G. Ya. Dubur and Ya. R. Uldrikis, Khim. Geterotsikl. Soedin., No. 1, 83 (1970).
9. H. Meyer, D. Scherling, and W. Karl, Arzneim. Forsch., **33**, 1528 (1983).
10. H. Kuehnis, Pat. Appl. 111,455 Eur.; Chem. Abs., **101**, 191875 (1984).
11. S. Goldmann, F. Bossert, H. Bischoff, D. Petzinna, W. Puls, and K. Schlossmann, Offenleg. 3,410,645 BRD; Chem. Abs., **104**, 88513 (1986).