Pyranopyrazoles. II (1).
Synthesis and Reactions of 1*H*,6*H*-Pyrano[2,3-*c*]pyrazol-6-ones

Misbahul Ain Khan* and Alina Guerra Cosenza (2)

Seção de Quimica, Instituto Militar de Engenharia, Urca,
22290 Rio de Janeiro, RJ, Brasil

Gwynn Pennant Ellis

Department of Chemistry, University of Wales Institute of Science and Technology,
Cardiff, CF1, 3NU, Wales, UK

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Various 1*H*,6*H*-pyrano[2,3-*c*]pyrazol-6-ones (III-XXIII) were obtained from β-keto esters and 1*H*-pyrazol-5-ones or hydrazines. Nitrations, chlorinations and brominations of these pyranopyrazoles were also carried out giving the corresponding derivatives (XXIV-LXIV). The pyrone ring is the more reactive one in these reactions and the preferred position of attack is the 5-position. The substitution products are formed by the addition-elimination route.

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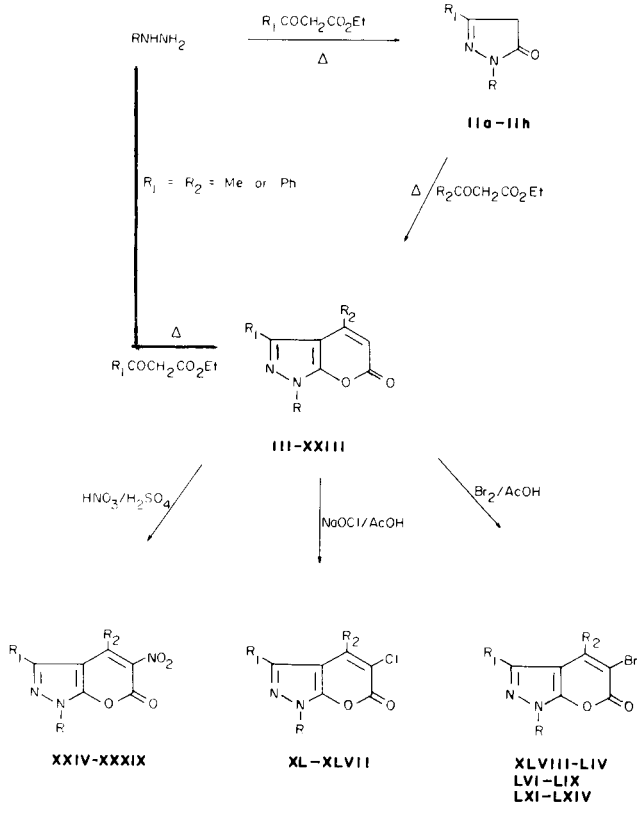
1*H*,6*H*-Pyrano[2,3-*c*]pyrazol-6-one (I) may be regarded as being isoelectronic with coumarin, the benzene ring of the latter having been replaced by the pyrazole ring. Various derivatives of I were previously obtained by other workers, generally incidental to some other work or as by-products (3). More recently, some derivatives of this system were shown to be good vasodialators, hypotensive and hypoglycemic agents (4). However, no systematic work as to their preparation and chemical reactivity has been reported and as such we would like to report our findings and compare these with the reactivity of coumarin.

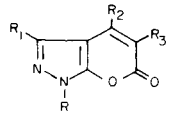
Scheme I



Derivatives of I were prepared from hydrazines and β-keto esters in two ways (Scheme 1). When hydrazine was treated with a β-keto ester in equimolar quantities, 1*H*-pyrazol-5-ones (IIa-IIh) were the products (5) which on condensation with a different β-keto ester (method A) gave 1*H*,6*H*-pyrano[2,3-*c*]pyrazol-6-ones containing different substituents at the 3 and 4 positions. While derivatives of I where the 3 and 4 position bear identical groups were easily obtained by heating a hydrazine with an excess (>2 moles) of a β-keto ester (method B). The identity of 1*H*,6*H*-pyrano[2,3-*c*]pyrazol-6-ones (III-XXIII) thus obtained was confirmed through their elemental analyses and spectra (Tables 1 and 2). The infrared (ir) spectra show the expected lactone carbonyl absorption peaks between 1710 and 1780 cm^{-1}. The proton magnetic resonance (pmr) spectra contain a signal between δ 5.75 and 5.95 which is ascribed to the proton of the 5 position of the 1*H*,6*H*-pyrano[2.3-*c*]pyrazol-6-one system (compare with the proton at the 3 position of coumarin which shows a signal at 6.42 (6)). In the pmr spectra of 1*H*,6*H*-pyrano[2,3-*c*]pyrazol-6-ones containing a methyl group at the 4 position, the signal for the 5 proton appears as a quartet (J = 1.2 Hz) due to its coupling with the methyl group which appears as a doublet (J = 1.2 Hz). The yields in these syntheses were generally good except in a few cases (9% for X). In some condensations using ethyl benzoylacetate, formation of acetophenone was detected. This probably results from the decomposition of ethyl benzoylacetate. In an attempted condensation of 1,3-diphenyl-1*H*-pyrazol-5-one with ethyl benzoylacetate, the expected 1,3,5-triphenyl-1*H*,6*H*-pyrano[2,3-*c*]pyrazol-6-one was not obtained but instead the ester (LXV) was isolated in 15% yield. The ester LXV was characterized through its elemental analysis and pmr spectrum which showed a singlet at δ 3.68 for two methyl-

Table 1

1*H*,6*H*-Pyrano[2,3-*c*]pyrazol-6-ones



Compound No. and Substituent	Method (a)	Yield (%)	Mp °C (solvent)	Formula	Elemental Analyses (b) C	H	N
III R = R_3 = H, R_1 = R_2 = Me	A	80	245 (c) (acetic acid)	—	—	—	—
IV R = R_1 = R_3 = H, R_2 = Me	A	42	207 (ethanol)	$C_7H_6N_2O_2$	55.74 (56.00)	4.03 (4.03)	18.40 (18.66)
V R = R_3 = H, R_1 = Me, R_2 = Ph	A	60	189 (acetic acid)	$C_{13}H_{10}N_2O_2$	68.98 (69.02)	4.54 (4.46)	12.10 (12.38)
VI R = R_3 = H, R_1 = Ph, R_2 = Me	A	82	190-191 (d) (ethanol)	—	—	—	—
VII R = R_1 = R_2 = Me, R_3 = H	A	60	175-176 (e) (ethanol)	—	—	—	—
VIII R = R_1 = Me, R_2 = Ph, R_3 = H	A	26	158 (ethanol)	$C_{14}H_{12}N_2O_2$	69.96 (69.99)	5.01 (5.03)	11.58 (11.66)
IX R = R_2 = Me, R_1 = Ph, R_3 = H	A	93	163-164 (ethanol)	$C_{14}H_{12}N_2O_2$	69.72 (69.99)	5.07 (5.03)	11.45 (11.66)
X R = Me, R_1 = R_2 = Ph, R_3 = H	A	9	203 (acetic acid)	$C_{19}H_{14}N_2O_2$	75.51 (75.48)	4.67 (4.70)	9.14 (9.27)
XI R = Ph, R_1 = R_2 = Me, R_3 = H	B	92	145 (f) (ethanol)	—	—	—	—
XII R = Ph, R_1 = R_3 = H, R_2 = Me	A	62	137-138 (ethanol)	$C_{13}H_{10}N_2O_2$	68.93 (69.02)	4.39 (4.46)	12.04 (12.38)
XIII R = R_2 = Ph, R_1 = R_3 = H	A	67	175-176 (ethanol)	$C_{18}H_{12}N_2O_2$	75.04 (74.99)	4.25 (4.20)	9.53 (9.27)
XIV R = R_2 = Ph, R_1 = Me, R_3 = H	A	44	140 (ethanol)	$C_{19}H_{14}N_2O_2$	75.58 (75.48)	4.83 (4.67)	9.28 (9.27)
XV R = R_1 = Ph, R_2 = Me, R_3 = H	A	39	211 (g) (ethanol)	—	—	—	—
XVI R = *o*-MeC_6H_4, R_1 = R_2 = Me, R_3 = H	B	61	170 (acetic acid)	$C_{15}H_{14}N_2O_2$	70.59 (70.85)	5.70 (5.55)	11.13 (11.02)
XVII R = *m*-MeC_6H_4, R_1 = R_2 = Me, R_3 = H	A	49	155 (acetic acid)	$C_{15}H_{14}N_2O_2$	71.02 (70.85)	5.65 (5.55)	10.91 (11.02)
XVIII R = *p*-MeC_6H_4, R_1 = R_2 = Me, R_3 = H	A	86	181-182 (acetic acid)	$C_{15}H_{14}N_2O_2$	70.95 (70.85)	5.59 (5.55)	11.10 (11.02)
XIX R = *o*-ClC_6H_4, R_1 = R_2 = Me, R_3 = H	A	40	126 (acetic acid)	$C_{14}H_{11}ClN_2O_2$	60.97 (61.21)	4.04 (4.04)	10.23 (10.23)
XX R = *p*-ClC_6H_4, R_1 = R_2 = Me, R_3 = H	A	83	180 (ethanol)	$C_{14}H_{11}ClN_2O_2$	61.07 (61.21)	4.03 (4.04)	10.02 (10.20)
XXI R = *o*-$NO_2C_6H_4$, R_1 = R_2 = Me, R_3 = H	B	61	210 (acetic acid)	$C_{14}H_{11}N_3O_4$	58.70 (58.95)	3.98 (3.89)	14.48 (14.73)
XXII R = *m*-$NO_2C_6H_4$, R_1 = R_2 = Me, R_3 = H	B	84	206 (acetic acid)	$C_{14}H_{11}N_3O_4$	58.80 (58.95)	3.93 (3.89)	14.53 (14.73)
XXIII R = *p*-$NO_2C_6H_4$, R_1 = R_2 = Me, R_3 = H	B	85	199-200 (acetic acid)	$C_{14}H_{11}N_3O_4$	58.71 (58.95)	3.82 (3.89)	14.36 (14.73)
XXIV R = H, R_1 = R_2 = Me, R_3 = NO_2	C	89	201-203 (acetic acid)	$C_8H_7N_3O_4$	45.76 (45.94)	3.40 (3.37)	20.24 (20.09)
XXV R = H, R_1 = *p*-$NO_2C_6H_4$, R_2 = Me, R_3 = NO_2	C	60	216 dec (ethanol)	$C_{13}H_8N_4O_6$	49.50 (49.36)	2.37 (2.53)	17.89 (17.71)
XXVI R = R_1 = Me, R_2 = *p*-$NO_2C_6H_4$, R_3 = NO_2	C	78	197 (ethanol)	$C_{14}H_{10}N_4O_6$	50.79 (50.91)	3.21 (3.05)	16.73 (16.97)
XXVII R = R_2 = Me, R_1 = *p*-$NO_2C_6H_4$, R_3 = NO_2	C	68	180 dec (ethanol)	$C_{14}H_{10}N_4O_6$	51.27 (50.91)	3.37 (3.05)	17.06 (16.97)

Table 1, continued

1*H*,6*H*-Pyrano[2,3-*c*]pyrazol-6-ones

Compound No. and Substituent	Method (a)	Yield (%)	Mp °C (solvent)	Formula	Elemental Analyses (b) C	H	N
XXVIII R = Ph, R_1 = R_2 = Me, R_3 = NO_2	D	47	179 (acetic acid)	$C_{14}H_{11}N_3O_4$	59.12 (58.95)	4.13 (3.89)	14.79 (14.73)
XXIX R = *p*-$NO_2C_6H_4$, R_1 = R_2 = Me, R_3 = NO_2	C, D	89	208-209 (ethyl acetate)	$C_{14}H_{10}N_4O_6$	51.04 (50.91)	3.11 (3.05)	17.02 (16.97)
XXX R = *p*-$NO_2C_6H_4$, R_1 = R_3 = NO_2, R_2 = Me	C	74	183 dec (acetic acid)	$C_{13}H_7N_5O_8$	42.97 (43.22)	2.01 (1.95)	19.03 (19.39)
XXXI R = R_2 = *p*-$NO_2C_6H_4$, R_1 = R_3 = NO_2	C	83	140 dec (ethanol)	$C_{18}H_8N_6O_{10}$	45.99 (46.15)	1.59 (1.71)	17.84 (17.95)
XXXII R = R_2 = *p*-$NO_2C_6H_4$, R_1 = Me, R_3 = NO_2	C	94	192 (acetic acid)	$C_{19}H_{11}N_5O_8$	51.65 (52.18)	2.63 (2.54)	15.93 (16.02)
XXXIII R = R_1 = *p*-$NO_2C_6H_4$, R_2 = Me, R_3 = NO_2	C	97	220 dec (ethyl acetate)	$C_{19}H_{11}N_5O_8$	52.41 (52.18)	2.67 (2.54)	15.84 (16.02)
XXXIV R = 2,4-$MeNO_2C_6H_3$, R_1 = R_2 = Me, R_3 = NO_2	C	99	195 (acetic acid)	$C_{15}H_{12}N_4O_6$	51.87 (52.33)	3.88 (3.51)	16.09 (16.27)
XXXV R = 3,4-$MeNO_2C_6H_3$, R_1 = R_2 = Me, R_3 = NO_2	C	87	191-192 (acetic acid)	$C_{15}H_{12}N_4O_6$	51.94 (52.33)	3.68 (3.51)	16.17 (16.27)
XXXVI R = 3,4-$NO_2C_6H_3$, R_1 = R_2 = Me, R_3 = NO_2	C	82	177 (acetic acid)	$C_{15}H_{12}N_4O_6$	52.27 (52.33)	3.55 (3.51)	16.09 (16.27)
XXXVII R = 2,4-$ClNO_2C_6H_3$, R_1 = R_2 = Me, R_3 = NO_2	C	82	245 (acetic acid)	$C_{14}H_{19}ClN_4O_6$	46.32 (46.11)	2.53 (2.49)	15.14 (15.36)
XXXVIII R [5] 2,4-$NO_2ClC_6H_3$, R_1 = R_2 = Me, R_3 = NO_2	C	90	159 (acetic acid)	$C_{14}H_{19}ClN_4O_6$	46.39 (46.11)	2.52 (2.49)	15.63 (15.36)
XXXIX R = *m*-$NO_2C_6H_4$, R_1 = R_2 = Me, R_3 = NO_2	C	93	158 (acetic acid)	$C_{14}H_{10}N_4O_6$	51.01 (50.91)	3.20 (3.05)	16.77 (16.97)
XL R = H, R_1 = R_2 = Me, R_3 = Cl	E	68	280-282 (acetic acid)	$C_8H_7ClN_2O_2$	48.52 (48.36)	3.41 (3.53)	13.97 (14.11)
XLI R = H, R_1 = Ph, R_2 = Me, R_3 = Cl	E	63	229 (ethanol)	$C_{13}H_9ClN_2O_2$	59.81 (59.90)	3.69 (3.48)	10.63 (10.75)
XLII R = R_1 = R_2 = Me, R_3 = Cl	E	31	181 (acetic acid)	$C_9H_9ClN_2O_2$	50.82 (50.84)	4.32 (4.27)	13.14 (13.18)
XLIII R = Ph, R_1 = R_2 = Me, R_3 = Cl	E	72	158 (acetic acid/ water)	$C_{14}H_{11}ClN_2O_2$	61.60 (61.21)	4.15 (4.04)	10.14 (10.20)
XLIV R = Ph, R_1 = H, R_2 = Me, R_3 = Cl	E	93	149 (ethanol)	$C_{13}H_9ClN_2O_2$	59.50 (59.90)	3.68 (3.48)	11.06 (10.79)
XLV R = *o*-MeC_6H_4, R_1 = R_2 = Me, R_3 = Cl	E	99	189 (acetic acid)	$C_{15}H_{13}ClN_2O_2$	61.89 (62.40)	4.45 (4.54)	9.51 (9.70)
XLVI R = *p*-MeC_6H_4, R_1 = R_2 = Me, R_3 = Cl	E	95	175 (acetic acid)	$C_{15}H_{13}ClN_2O_2$	62.20 (62.40)	4.48 (4.54)	9.50 (9.70)
XLVII R = *p*-$NO_2C_6H_4$, R_1 = R_2 = Me, R_3 = Cl	E	62	253 (acetic acid)	$C_{14}H_{10}ClN_3O_4$	52.37 (52.60)	3.18 (3.15)	13.08 (13.14)
XLVIII R = H, R_1 = R_2 = Me, R_3 = Br	F	76	191-192 (acetic acid)	$C_8H_7BrN_2O_2$	39.33 (39.53)	3.03 (2.90)	11.62 (11.53)
XLIX R = H, R_1 = Ph, R_2 = Me, R_3 = Br	F	65	243-244 (ethanol)	$C_{13}H_9BrN_2O_2$	50.98 (51.17)	3.00 (2.97)	8.99 (9.18)
L R = R_1 = R_2 = Me, R_3 = Br	F	30	184 (acetic acid)	$C_9H_9BrN_2O_2$	42.16 (42.05)	3.59 (3.53)	10.71 (10.90)

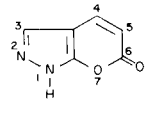
Table 1, continued

1*H*,6*H*-Pyrano[2,3-*c*]pyrazol-6-ones

Compound No. and Substituent	Method (a)	Yield (%)	Mp °C (solvent)	Formula	Elemental Analyses (b) C	H	N
LI R = R_1 = Me, R_2 = Ph, R_3 = Br	F	79	140 (acetic acid)	$C_{14}H_{11}BrN_2O_2$	52.54 (52.69)	3.60 (3.47)	8.79 (8.78)
LII R = R_2 = Me, R_1 = Ph, R_3 = Br	F	55	177-178 (ethanol)	$C_{14}H_{11}BrN_2O_2$	52.57 (52.69)	3.50 (3.47)	8.90 (8.78)
LIII R = Me, R_1 = R_2 = Ph, R_3 = Br	F	95	212 (acetic acid)	$C_{19}H_{13}BrN_2O_2$	60.00 (59.86)	3.51 (3.44)	7.35 (7.35)
LIV R = Ph, R_1 = R_2 = Me, R_3 = Br	F	87	184 (acetic acid)	$C_{14}H_{11}BrN_2O_2$	52.86 (52.69)	3.51 (3.47)	8.65 (8.78)
LV R = Ph, R_1 = H, R_2 = Me, R_3 = Br	F	(h)	205-206 (ethanol)	$C_{13}H_9BrN_2O_2$	50.93 (51.15)	2.82 (2.95)	9.34 (9.18)
LVI R = R_2 = Ph, R_1 = H, R_3 = Br	F	96	147 (acetic acid)	$C_{18}H_{11}BrN_2O_2$	59.00 (58.88)	3.17 (3.02)	7.78 (7.63)
LVII R = R_2 = Ph, R_1 = Me, R_3 = Br	F	95	238 (acetic acid)	$C_{19}H_{13}BrN_2O_2$	59.78 (59.86)	3.26 (3.44)	7.16 (7.35)
LVIII R = R_1 = Ph, R_2 = Me, R_3 = Br	F	(h)	214 (ethanol)	$C_{19}H_{13}BrN_2O_2$	60.05 (59.86)	3.63 (3.44)	7.30 (7.35)
LIX R = *o*-MeC_6H_4, R_1 = R_2 = Me, R_3 = Br	F	96	184-185 (acetic acid)	$C_{15}H_{13}BrN_2O_2$	54.13 (54.05)	3.98 (3.90)	8.63 (8.41)
LX R = *m*-MeC_6H_4, R_1 = R_2 = Me, R_3 = Br	F	(h)	178-179 (ethanol)	$C_{15}H_{13}BrN_2O_2$	53.62 (54.05)	4.05 (3.90)	8.68 (8.41)
LXI R = *p*-MeC_6H_4, R_1 = R_2 = Me, R_3 = Br	F	85	155-157 (acetic acid)	$C_{15}H_{13}BrN_2O_2$	54.21 (54.05)	3.82 (3.90)	8.31 (8.41)
LXII R = *p*-ClC_6H_4, R_1 = R_2 = Me, R_3 = Br	F	95	206-208 (acetic acid)	$C_{14}H_{10}BrClN_2O_2$	47.30 (47.55)	2.87 (2.85)	7.76 (7.92)
LXIII R = *m*-$NO_2C_6H_4$, R_1 = R_2 = Me, R_3 = Br	F	62	222 (acetic acid)	$C_{14}H_{10}BrN_3O_4$	46.17 (46.17)	2.88 (2.77)	11.42 (11.54)
LXIV R = *p*-$NO_2C_6H_4$, R_1 = R_2 = Me, R_3 = Br	F	90	263 (acetic acid)	$C_{14}H_{10}BrN_3O_4$	46.22 (46.17)	2.80 (2.77)	11.48 (11.54)

(a) See experimental. (b) Figures in parentheses refer to the calculated values. (c) Lit (3a,3g) mp 245°. (d) Lit (3b) mp 191-193°. (e) Lit (3*l*) mp 167°. (f) Lit (3c) mp 145°. (g) Lit (3b) mp 195-197°. (h) Obtained by dehydrobromination of the reaction mixture.

ene protons. All attempts to cyclize this ester failed. In a reaction of *m*-nitrophenylhydrazine hydrochloride with ethyl acetoacetate in large excess, in addition to the expected XXII, dehydroacetic acid was isolated in 45% yield. The dehydroacetic acid arises from the auto-condensation of ethyl acetoacetate in the presence of hydrochloric acid (7).



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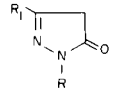
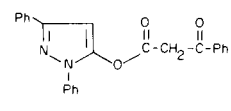
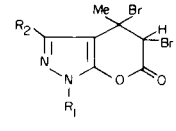


IIa-IIh

a, R = H, R_1 = Me
b, R = Ph, R_1 = Me
c, R = Me, R_1 = Ph
d, R = Ph, R_1 = H
e, R = R_1 = H
f, R = R_1 = Me
g, R = R_1 = Ph
h, R = H, R_1 = Ph



LXV



LXVIa-LXVIc

a, R_1 = Ph, R_2 = H
b, R_1 = R_2 = Ph
c, R_1 = *m*-MeC_6H_4, R_2 = Me

Nitration of these 1*H*,6*H*-pyrano[2,3-*c*]pyrazol-6-ones with "mixed acid" (niric and sulfuric acid) normally gave nitration at the 5 position which was evidenced by the disappearance of the signal between δ 5.75 and 5.95 in their pmr spectra (Scheme 1). But 3-unsubstituted 1*H*,6*H*-pyrano[2,3-*c*]pyrazol-6-ones (XII and XIII) gave 3,5-dinitro derivatives XXX and XXXI. The phenyl groups in the 1 position (XI-XV), the 3 position (VI, IX, X, XV) or the 4 position (VIII, XIII, XIV) were also found to be nitrated in the *para* position under these reaction conditions. The

Table 2

Spectroscopic Properties of 1*H*,6*H*-Pyrano[2,3-*c*]pyrazol-6-ones

Compound No.	PMR δ (J in Hz) H-1/R	H-3/R_1	R_2	H-5/R_3	Solvent	Infrared (cm^{-1})
III	12.70-13.70, br	2.48, s	2.34, d (1.2)	5.78, q (1.2)	DMSO-d_6	3250 (NH), 1720 (C=O), 1610, 1520, 1200, 1120, 1100, 930, 760
IV	—	8.08, s	2.36, d (1.2)	5.84, q (1.2)	acetone-d_6	3250 (NH), 1710 (C=O), 1610, 1550, 1130, 1110, 860, 740
V	—	2.16, s	7.54, s	5.84, s	acetone-d_6	3250 (NH), 1730 (C=O), 1600, 1560, 1500, 1280, 870, 830, 750, 730
VI	—	7.52, s	2.10, d (1.2)	5.80, q (1.2)	deuterio-chloroform	3550 (NH), 1710 (C=O), 1630, 1600, 1550, 1210, 920, 830, 770, 750
VII	3.74, s	2.38, s	2.34, d (1.2)	5.62, q (1.2)	deuterio-chloroform	1740 (C=O), 1600, 1570, 1420, 1380, 1130, 840, 738
VIII	3.82, s	2.02, s	7.46, s	5.84, s	deuterio-chloroform	1740 (C=O), 1560, 1520, 1430, 1120, 830, 740, 700
IX	3.88, s	7.48, s	2.16, d (1.2)	5.78, q (1.2)	deuterio-chloroform	1740 (C=O), 1600, 1560, 1520, 1460, 850, 820, 760
X	3.92, s	7.05, s	7.20, s	5.90, s	acetone-d_6	1740 (C=O), 1600, 1570, 1440, 1380, 1110, 840, 760
XI	7.20-7.80, m	2.40, s	2.30, d (1.2)	5.78, q (1.2)	deuterio-chloroform	1774 (C=O), 1558, 1520, 1440, 820, 720
XII	7.20-8.00, m	7.20-8.00, m	2.36, d (1.2)	5.82, q (1.2)	dueterio-chloroform	1740 (C=O), 1580, 1520, 1420, 1320, 1210, 960, 840
XIII	7.20-7.96, m	7.20-7.96, m	7.20-7.96, m	6.12, s	deuterio-chloroform	1740 (C=O), 1600, 1540, 1500, 980, 750
XIV	7.20-8.00, m	2.06, s	7.20-8.00, m	5.90, s	deuterio-chloroform	1740 (C=O), 1580, 1540, 1480, 1160, 1060, 830, 760
XV	7.20-8.00, m	7.20-8.00, m	2.14, d (1.2)	5.86, q (1.2)	deuterio-chloroform	1760 (C=O), 1620, 1520, 1460, 1400, 900, 760
XVI	6.80-7.70, m 2.42, s	2.30-3.36, m	2.30-2.36, m	5.70, q (1.2)	deuterio-chloroform	1750 (C=O), 1620, 1560, 1380, 1110, 840, 800, 780
XVII	7.00-7.80, m 2.50, s	2.35-2.40, m	2.35-2.40, m	5.76, q (1.2)	deuterio-chloroform	1750 (C=O), 1620, 1560, 1460, 1380, 1110, 840, 800
XVIII	7.20, d, 7.70, d (8), 2.46, s	2.35-2.40, m	2.35-2.40, m	5.74, q (1.2)	deuterio-chloroform	1740 (C=O), 1620, 1580, 1380, 840, 800
XIX	7.20-7.60, m	2.50, s	2.40, d (1.2)	5.75, q (1.2)	deuterio-chloroform	1730 (C=O), 1600, 1560, 1480, 1040, 840, 820, 740
XX	7.36, d, 7.80, d (9)	2.48, s	2.38, d (1.2)	5.76, q (1.2)	deuterio-chloroform	1750 (C=O), 1600, 1580, 1540, 1480, 1390, 1000, 840
XXI	7.20-8.30, m	2.45, s	2.45, d (1.2)	5.95, q (1.2)	DMSO-d_6	1750 (C=O), 1610, 1550 (NO_2), 1440, 1390, 1360 (NO_2), 1100, 780, 750, 730
XXII	7.20-8.80, m	2.53, s	2.46, d (1.2)	5.84, q (1.2)	deuterio-chloroform	1770 (C=O), 1520 (NO_2), 1440, 1380, 1350 (NO_2), 1110, 720
XXIII	7.98, d, 8.38 d (9)	2.40-2.50, m	2.40-2.50, m	5.95, q (1.2)	DMSO-d_6	1760 (C=O), 1630, 1590, 1550 (NO_2), 1520, 1380, 1340 (NO_2), 1100, 850
XXIV	13.30-13.60, br	2.56, s	2.48, s	—	DMSO-d_6	3580 (NH), 1730 (C=O), 1600, 1550 (NO_2), 1540, 1380 (NO_2), 1160, 1030, 980
XXV	—	7.80-8.60, m	2.30, s	—	acetone-d_6	3550 (NH), 1740 (C=O), 1600, 1580, 1520 (NO_2), 1460, 1360 (NO_2), 760, 720
XXVI	3.86, s	2.78, s	7.54, d, 8.36, d (9)	—	deuterio-chloroform	2950, 1760 (C=O), 1600, 1540 (NO_2), 1480, 1360 (NO_2), 720
XXVII	3.98, s	7.68, d, 8.32, d (9)	2.28, s	—	deuterio-chloroform	1750 (C=O), 1600, 1580, 1530 (NO_2), 1400, 1370 (NO_2), 760, 700
XXVIII	7.40-8.00, m	2.60, s	2.60, s	—	acetone-d_6	1750 (C=O), 1620, 1600, 1545 (NO_2), 1450, 1370, 1350 (NO_2), 1110, 860, 850
XXIX	8.02, d, 8.44, d (9)	2.58, s	2.58, s	—	DMSO-d_6	1760 (C=O), 1630, 1618, 1510 (NO_2), 1400, 1300 (NO_2), 1110
XXX	8.18, d, 8.48, d (9)	—	2.64, s	—	acetone-d_6	1760 (C=O), 1600, 1580, 1540 (NO_2), 1520, 1340 (NO_2), 960

Table 2, continued

Spectroscopic Properties of 1*H*,6*H*-Pyrano[2,3-c]pyrazol-6-ones

Compound No.	PMR δ (J in Hz) H-1/R	H-3/R_1	R_2	H-5/R_3	Solvent	Infrared (cm^{-1})
XXXI	8.02, d, 8.22, d, 8.45, d, 8.50, d (9)	—	8.02, d, 8.22, d 8.45, d, 8.50, d (9)	—	acetone-d_6	1760 (C=O), 1600, 1520 (NO_2), 1400, 1340 (NO_2), 840, 720
XXXII	7.60-8.70, m	1.78, s	7.60-8.70, m	—	DMSO-d_6	1770 (C=O), 1620, 1600, 1530 (NO_2), 1400, 1340 (NO_2), 860, 770, 740
XXXIII	7.80-8.70, m	7.80-8.70, m	2.30, s	—	DMSO-d_6	1780 (C=O), 1650, 1540 (NO_2), 1520, 1440, 1400, 1360 (NO_2), 860
XXXIV	7.60-8.30, m 2.62, s	2.60, s	1.90, s	—	DMSO-d_6	1760 (C=O), 1600, 1550 (NO_2), 1520, 1460, 1380, 1340 (NO_2), 1300, 860
XXXV	7.70-8.30, m 2.70, s	2.60, s	2.08, s	—	deuterio-chloroform	1770 (C=O), 1610, 1550 (NO_2), 1520, 1440, 1380, 1330 (NO_2), 820, 740
XXXVI	7.20-8.50, m 2.62, s	2.60, s	2.60, s	—	deuterio-chloroform	1760 (C=O), 1620, 1540 (NO_2), 1460, 1340 (NO_2), 1020, 740, 700
XXXVII	8.00-8.60, m	2.64, s	2.58, s	—	DMSO-d_6	1770 (C=O), 1600, 1560 (NO_2), 1520, 1480, 1350)NO_2), 1220, 1110, 880
XXXVIII	7.80-8.60, m	3.60, s	3.54, s	—	acetone-d_6	1760 (C=O), 1600, 1540 (NO_2), 1480, 1350 (NO_2), 1100, 1000, 820, 750
XXXIX	7.70-8.70, m	2.60, s	2.56, s	—	DMSO-d_6	1780 (C=O), 1620, 1600, 1540 (NO_2), 1360 (NO_2), 740, 720
XL	12.90-13.20, br	2.46, s	2.44, s	—	DMSO-d_6	3290 (NH), 1720 (C=O), 1600, 1570, 1200, 740
XLI	11.90-13.00, br	7.58, s	2.24, s	—	acetone-d_6	3350 (NH), 1720, (C=O), 1620, 1600, 1580, 1170, 980, 760, 740
XLII	3.74, s	2.52, s	2.44, s	—	deuterio-chloroform	2950, 1740 (C=O), 1580, 1380, 930, 790, 730
XLIII	7.20-7.80, m	2.52, s	2.48, s	—	deuterio-chloroform	1730 (C=O), 1600, 1480, 1320, 920, 760, 740
XLIV	7.00-8,00, m	7.00-8.00, m	2.50, s	—	deuterio-chloroform	1750 (C=O), 1600, 1560, 1520, 960, 740, 720
XLV	7.02-7.20, m 2.60, s	2.54, s	2.44, s	—	deuterio-chloroform	1750 (C=O), 1600, 1550, 1380, 920, 800, 760
XLVI	7.02, d, 7.18, d (9), 2.52, s	2.50, s	2.38, s	—	deuterio-chloroform	1740 (C=O), 1620, 1560, 1470, 1400, 930, 820, 740
XLVII	7.62-8.45, m	3.04, s	3.04, s	—	DMSO-d_6 (80°)	1745 (C=O), 1620, 1600, 1545 (NO_2), 1510, 1340 (NO_2), 1110, 930, 860
XLVIII	13.00-13.30, br	2.50, s	2.50, s	—	DMSO-d_6	3580 (NH), 1730 (C=O), 1600, 1580, 1540, 960, 740, 720
XLIX	13.10-13.90, br	7.68, s	2.28, s	—	acetone-d_6	3350 (NH), 1750 (C=O), 1600, 1560, 1520, 1460, 950, 750
L	3.74, s	2.52, s	2.44, s	—	deuterio-chloroform	2950, 1740 (C=O), 1580, 1360, 920, 760, 740
LI	3.80, s	1.70, s	7.12-7.60, m	—	deuterio-chloroform	2960, 1760 (C=O), 1580, 1510, 1440, 1180, 900
LII	3.90, s	7.44, s	2.28, s	—	deuterio-chloroform	1740 (C=O), 1600, 1580, 1500, 1400, 930, 780, 740
LIII	3.88, s	6.60-7.50, m	6.60-7.50, m	—	DMSO-d_6	1740 (C=O), 1580, 1560, 1495, 1390, 1110, 860, 760
LIV	7.30-7.90, m	2.52, s	2.46, s	—	deuterio-chloroform	1735 (C=O), 1600, 1540, 1450, 1380, 930, 780, 760
LV	7.60-8.00, m	7.60-8.00, m	2.60, s	—	deuterio-chloroform	—
LVI	7.14-7.94, m	7.14-7.94, m	7.14-7.94, m	—	deuterio-chloroform	1740 (C=O), 1600, 1540, 1400, 740, 720
LVII	7.24-8.00, m	1.80, s	7.24-8.00, m	—	deuterio-chloroform	1750 (C=O), 1580, 1530, 1460, 1060, 940, 900, 760

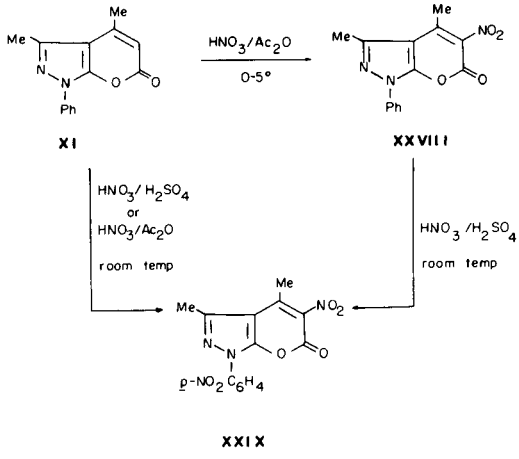
Table 2, continued

Spectroscopic Properties of 1*H*,6*H*-Pyrano[2,3-*c*]pyrazol-6-ones

Compound No.	PMR δ (J in Hz) H-1/R	H-3/R_1	R_2	H-5/R_3	Solvent	Infrared (cm^{-1})
LVIII	7.34-8.00, m	7.34-8.00, m	2.30, s	—	deuterio-chloroform	—
LIX	7.44-7.76, m 2.60, s	2.52, s	2.44, s	—	deuterio-chloroform	1750 (C=O), 1580, 1540, 1480, 1380, 1020, 900
LX	7.30-8.00, m 2.58, s	2.52, s	2.48, s	—	deuterio-chloroform	—
LXI	7.18, d, 7.62, d (9)	2.46, s	2.38, s	—	deuterio-chloroform	1740 (C=O), 1580, 1540, 1460, 1380, 1100, 900
LXII	7.36, d, 7.76, d (9)	2.58, s	2.50, s	—	deuterio-chloroform	1750 (C=O), 1540, 1400, 1360, 900, 760, 740
LXIII	8.08, d, 8.38, d (9)	2.62, s	2.54, s	—	deuterio-chloroform	1750 (C=O), 1600, 1580, 1530 (NO_2), 1460, 1380, 1350 (NO_2), 1340, 1100
LXIV	7.60-8.80, m	2.62, s	2.56, s	—	DMSO-d_6/deuteriochloroform, (70°)	2950, 1760 (C=O), 1540 (NO_2), 1520, 1350 (NO_2), 1100, 720

"*para* nitration" of these phenyl substituents of 1*H*,6*H*-pyrano[2,3-*c*]pyrazol-6-ones was confirmed by their pmr spectra (AB quartets). The nitration behaviour of the 1-, and 3-phenyl derivatives could be compared to that of 1,3-diphenylpyrazole where Lynch and Hung had found nitration occurring in the *para* positions (8). The 4-phenyl-1*H*,6*H*-pyrano[2,3-*c*]pyrazol-6-ones could be compared with cinnamic acid which has also been found to undergo nitration in the *para* position (9). The reagent and temperature dependance in the nitrations was also observed in the nitration of 3,4-dimethyl-1-phenyl-1*H*,6*H*-pyrano[2,3-*c*]pyrazol-6-one (XI) (Scheme 2). Nitration with

Scheme 2



"mixed acid" at ambient temperature gave a dinitro product XXIX where the 5 position of the 1*H*,6*H*-pyrano-[2,3-*c*]pyrazol-6-one system as well as the *para* position of the phenyl substituent was nitrated. However, when the nitration was carried out with acetyl nitrate below 0°, the only product isolated was 5-nitro derivative XXVIII where mononitration had occurred only in the 5 position. This was confirmed from its pmr spectrum where the characteristic signal of C_5-proton at δ 5.78 had disappeared and the C_4-methyl signal had collapsed into a singlet at δ 2.60 and there was no change in the aromatic protons multiplet between δ 7.00 and 8.00. When the reaction temperature in the nitration with acetyl nitrate was raised, the dinitration product was formed together with the mononitration product and at 20° exclusive formation of the dinitro compound XXIX was observed. This dinitro product was identical with the compound isolated in the nitration of either XI or XXII by "mixed acid". The various nitro derivatives XXIV-XXXIX thus obtained were recorded in the Tables 1 and 2.

The chlorination of some 1*H*,6*H*-pyrano[2,3-*c*]pyrazol-6-ones was carried out by means of hypochlorous acid in acetic acid and the corresponding 5-chloro derivatives XL-XLVII were obtained (Scheme 1). These chloro derivatives were characterized by their elemental analyses and pmr spectra (Tables 1 and 2).

The bromination (using bromine in acetic acid) of various 1*H*,6*H*-pyrano[2,3-*c*]pyrazol-6-ones led to their respective 5-bromo derivatives XLVIII-LIV, LVI, LVII, LIX, LXI-LXIV (Scheme 1) which were identified through their elemental analyses and pmr spectra (Tables 1 and 2). The bromination products of XII, XV and XVII gave somewhat unsatisfactory elemental analyses. Their pmr spectra exhibited all the signals expected of 5-bromo derivatives. However in the region of δ 4.00-5.00, a sharp singlet was observed. This could be ascribed to a proton on the same carbon atom containing a bromine atom and this was compatible with the structures LXVIa-LXVIc. These dibromo compounds could arise by the addition of a bromine molecule to the 4,5 double bond of the 1*H*,6*H*-

pyrano[2,3-*c*]pyrazol-6-one system. The addition of bromine to the double bond of the α-pyrone ring in coumarin leading to 3,4-dibromo-3,4-dihydrocoumarin is a well known reaction and the dehydrobromination with pyridine is the route used for the preparation of 3-bromocoumarin (10). When the mixture of 5-bromo-1,3-diphenyl-3-methyl-1*H*,6*H*-pyrano[2,3-*c*]pyrazol-6-one (LVIII) and 4,5-dibromo-4,5-dihydro-1,3-diphenyl-3-methyl-1*H*,6*H*-pyrano[2,3-*c*]pyrazol-6-one (LXVIb) (obtained from the bromination of XV) was treated with pyridine in boiling alcohol, elimination occurred to give exclusively LVIII, the formation of which was confirmed by the disappearance of the singlet at δ 4.32 in the pmr spectrum of the product of the elimination reaction. The bromo derivatives LV and LX were similarly obtained by dehydrobrominations of the mixtures formed in the brominations of XII and XVII, respectively. No efforts, however, were made to isolate LXVIa-LXVIc.

In view of the results of these brominations it seems reasonable to assume that bromination as well as the nitration of pyrano[2,3-*c*]pyrazol-6-one system occurs by an addition-elimination mechanism, the *N*-2 ("pyridine type") of the pyrazole ring of the system helping in the rapid elimination step. Further work will be needed to establish the mechanism of these reactions.

The reduction of 3,4-dimethyl-1-phenyl-1*H*,6*H*-pyrano-[2,3-*c*]pyrazol-6-one (XI) with palladium on charcoal under milder conditions was also attempted but without success. Under similar conditions the coumarin ring system is readily reduced to the corresponding 3,4-dihydrocoumarin (11).

EXPERIMENTAL

The pmr spectra were taken on a 60 MHz Hitachi Perkin-Elmer model R-20B using tetramethylsilane as an internal reference. Infrared absorption spectra were measured on a Perkin-Elmer model 180, samples were examined as potassium bromide pellets. The melting points were observed on a Fisher-Johns apparatus and are uncorrected.

The following 1*H*-pyrazol-5-ones were prepared according to the literature method: 3-methyl-1*H*-pyrazol-5-one (IIa), mp 212° (3o); 3-methyl-1-phenyl-1*H*-pyrazol-5-one (IIb), mp 126° (12); 1-methyl-3-phenyl-1*H*-pyrazol-5-one (IIc), mp 209° (13); 1-phenyl-1*H*-pyrazol-5-one (IId), mp 118° (14); 1*H*-pyrazol-5-one (IIe), mp 161° (15); 1,3-dimethyl-1*H*-pyrazol-5-one (IIf), mp 117° (16); 1,3-diphenyl-1*H*-pyrazol-5-one (IIg), mp 136° (17); and 3-phenyl-1*H*-pyrazol-5-one (IIh), mp 244° (18).

1*H*,6*H*-Pyrano[2,3-*c*]pyrazol-6-ones.

Method A.

An equimolar mixture of a 1*H*-pyrazol-5-one and a β-keto ester (ethyl acetoacetate or ethyl benzoylacetate) was heated at a temperature of 150-170° (oil bath) for one hour. The reaction mixture was cooled, diluted with ether and filtered. The residue was dissolved in an adequate solvent, treated with activated carbon and crystallized.

Method B.

One mole of the hydrazine and two moles of ethyl acetoacetate were heated together at a temperature of 120-130° (oil bath) for one hour (the ethanol formed during the reaction being allowed to escape) and then cooled and treated as described in Method A.

The 1*H*,6*H*-pyrano[2,3-*c*]pyrazol-6-ones (III-XXIII) obtained in these reactions are listed in Tables 1 and 2.

1,3-Diphenyl-1*H*-pyrazol-5-yl Benzoylacetate (LXV).

A mixture of 2 g of IIg and 4 g of ethyl benzoylacetate was heated for half an hour at a temperature of 150-170°. After cooling the reaction mixture was filtered and the residue crystallized from ethanol (activated carbon) to give 0.5 g (15%) of LXV, mp 142°; pmr (deuteriochloroform): δ 3.68 (s, -CH_2-), 7.00-8.00 (m, arom and H-4 of pyrazole); ir: 3000, 1710 (C=O), 1600, 1500, 1460, 1340, 1180, 1120, 760 cm^{-1}

Anal. Calcd. for $C_{24}H_{18}N_2O_3$: C, 75.38; H, 4.74; N, 7.33. Found: C, 75.39; H, 5.00, N, 7.60.

Nitration of 1*H*,6*H*-Pyrano[2,3-*c*]pyrazol-6-ones.

Method C (With Mixed Acid).

The nitration of III illustrates this method. A mixture of 5 ml of concentrated nitric acid and 5 ml of concentrated sulfuric acid was added dropwise to a solution of 5 g (30 mmoles) of III in 5 ml of concentrated sulfuric acid. The reaction mixture was maintained at room temperature for a period of half an hour and then poured over crushed ice, filtered, washed with ice-cold water and crystallized from acetic acid to give 5.7 g (89%) of XXIV, mp 201-203°.

Method D (With Acetyl Nitrate).

To a solution of 1 g (4 mmoles) of XI in 5 ml of acetic anhydride at 0° was added 2 ml of fuming nitric acid (d, 1.5) at such a rate that the temperature did not rise above 0° (dry ice cooling). After the addition of nitric acid was completed, the reaction mixture was allowed to stand for two hours at 0-5° then poured over crushed ice and left overnight, filtered, washed with cold water and crystallized from acetic acid (activated carbon) to give 0.55 g (47%) of XXVIII mp 179°.

Chlorination of 1*H*,6*H*-Pyrano[2,3-*c*]pyrazol-6-ones.

Method E.

A commercial solution of 5 ml of sodium hypochlorite (*ca.* 5%) was added dropwise to 2 mmoles of a 1*H*,6*H*-pyrano[2,3-*c*]pyrazol-6-one dissolved in 5 ml of acetic acid and stirred at room temperature for a period of half an hour. The reaction mixture was poured over crushed ice, filtered and washed thoroughly with water followed by crystallization from an appropriate solvent.

Bromination of 1*H*,6*H*-Pyrano[2,3-*c*]pyrazol-6-ones.

Method F.

To a solution of 5 mmoles of 1*H*,6*H*-pyrano[2,3-*c*]pyrazol-6-one in 2 to 5 ml of acetic acid there was added a solution of 0.5 ml of bromine in 2 ml of acetic acid and the mixture was stirred at room temperature for half an hour. The reaction mixture was poured over crushed ice, treated with a saturated solution of sodium bisulfite and filtered. The residue was washed thoroughly with water and crystallized from a suitable solvent.

Bromination of 4-Methyl-1-phenyl-1*H*,6*H*-pyrano[2,3-*c*]pyrazol-6-one (XII).

The bromination of XII was carried out according to the method F, by the addition of 0.5 ml of bromine dissolved in 2 ml of acetic acid to a solution of 0.16 g of XII in 2 ml of acetic acid. After crystallization from ethanol, 0.17 g of a mixture mp 146-149° consisting of equal quantities of 5-bromo-4-methyl-1-phenyl-1*H*,6*H*-pyrano[2,3-*c*]pyrazol-6-one (LV) and 4,5-dibromo-4,5-dihydro-4-methyl-1-phenyl-1*H*,6*H*-pyrano[2,3-*c*]pyrazol-6-one (LXVIa) was obtained; pmr (deuteriochloroform): δ 2.52 (s, CH_3), 4.54 (s, H-5), 7.20-7.96 (m, arom and H-3); ir: 1740 (C=O), 1600, 1560, 1520, 960,740, 720 cm^{-1}.

Anal. Calcd. for $C_{13}H_9N_2O_2Br$ + $C_{13}H_{10}N_2O_2Br_2$ (1:1): C, 45.08; H, 2.77; N, 8.01. Found: C, 45.00, H, 2.55; N 7.97.

Bromination of 1,3-Diphenyl-4-methyl-1*H*,6*H*-pyrano[2,3-*c*]pyrazol-6-one (XV).

From the bromination of 0.17 g of XV, there was obtained 0.22 g of a mixture of 5-bromo-1,3-diphenyl-4-methyl-1*H*,6*H*-pyrano[2,3-*c*]pyrazol-6-one (LVIII) and 4,5-dibromo-4,5-dihydro-1,3-diphenyl-1*H*,6*H*-pyrano-[2,3-*c*]pyrazol-6-one (LXVIb) which was crystallized from ethanol, mp 173-179°; pmr (deuteriochloroform): δ 2.38 (s, C*H*$_3$), 4.32 (s, H-5), 7.00-8.10 (m, arom); ir: 1740 (C=O), 1600, 1540, 1470, 1380, 920, 750 cm^{-1}.

Anal. Calcd. for $C_{19}H_{13}BrN_2O_2$ + $C_{19}H_{14}Br_2N_2O_2$ (1:): C, 54.19; H, 3.20; N, 6.64. Found: C, 55.83; H, 3.20; N, 6.89.

Bromination of 3,4-Dimethyl-1-*m*-tolyl-1*H*,6*H*-pyrano[2,3-*c*]pyrazol-6-one (XVII).

A similar bromination of 0.15 g of XVII gave, after crystallization from ethanol, an unequal mixture of 5-bromo-3,4-dimethyl-1-*m*-tolyl-1*H*,6*H*-pyrano[2,3-*c*]pyrazol-6-one (LX) and 4,5-dibromo-4,5-dihydro-3,4-dimethyl-1-*m*-tolyl-1*H*,6H-pyrano[2,3-*c*]pyrazol-6-one (LXVIc) mp 165-167°; pmr (acetone-d_6): 2.48 (s, C*H*$_3$), 2.62 (s, C*H*$_3$), 2.78 (s, C*H*$_3$), 4.78 (s, H-5), 7.40-8.20 (m, arom); ir: 1760 (C=O), 1560, 1450, 1380, 1040, 860, 800, 740 cm^{-1}.

Anal. Calcd. for $C_{15}H_{13}BrN_2O_2$ + $C_{15}H_{14}Br_2N_2O_2$ (1:1): C, 48.19; H, 3,62; N, 7.49. Found: C, 42.44; H, 3.03; N, 7.06.

Dehydrobrominations.

The mixtures of bromo and dibromo products obtained in the above brominations were dehydrobrominated as follows:

The mixture of the two products and 0.5 ml of pyridine in 5 ml of ethanol was heated under reflux for a period of thirty minutes, cooled, added to crushed ice, filtered and thoroughly washed with water and crystallized from ethanol to give the bromo derivatives LV, LVIII and LX (Tables 1 and 2).

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REFERENCES AND NOTES

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