Tetrahedron, 1963, Vol. 19, pp. 1577 to 1585. Pergamon Press Ltd. Printed in Northern Ireland

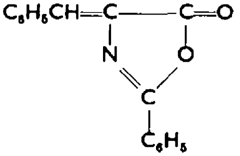
CLEAVAGE REACTIONS WITH 4-SUBSTITUTED ISOXAZOLIN-5-ONES

A. MUSTAFA, W. ASKER, A. H. HARHASH and N. A. L. KASSAB
The Department of Chemistry, Faculty of Science, Cairo University, U.A.R.

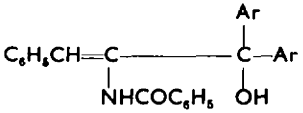
Abstract—The exocyclic double bond in 4-arylidene-3-methylisoxazolin-5-ones (IV) undergoes addition reactions with Grignard reagents and with aromatic hydrocarbons in the presence of aluminium chloride.

The behaviour of the hetero-ring in 4-substituted 3-methylisoxazolin-5-ones towards the action of hydrazines has been investigated. Whereas, the corresponding pyrazolines (X) are obtained in the case of hydrazine hydrate, the intermediate hydrazides (XI) have been successfully isolated in the case of phenylhydrazine. The hydrazides are readily cyclized under different experimental conditions to yield different products.

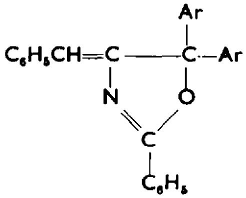
IT HAS been shown that, whereas the oxazolone ring in 2-phenyl-4-benzylidene-5(4H)oxazolone (I) is readily cleaved by the action of arylmagnesium halides to give 1,1-diaryl-2-benzamidocinnamyl alcohol (II) together with 2-phenyl-5,5-diaryl-4-benzylidene-2-oxazoline (III)[1], 4-benzylidene-3-methylisoxazolin-5-one (IVa) gives with phenylmagnesium bromide 4-benzhydryl-3-methylisooxazolin-5-one (Va)[2]. On the other hand, recently, Mustafa and Sallam[3] have shown that I, like IVa, reacts with alkyl- and aralkylmagnesium halides to give VI.



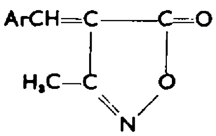
I



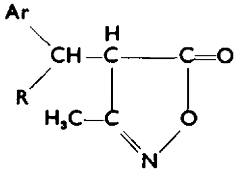
II



III



IVa, Ar = C_6H_5,
b, Ar = C_6H_4Cl-*p*,
c, Ar = $C_6H_4OCH_3$-*p*,



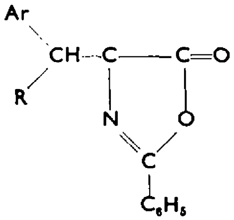
Va, Ar = R = C_6H_5
b, Ar = C_6H_5, R = $C_6H_4CH_3$-*p*,
c, Ar = C_6H_5, R = C_2H_5,
d, Ar = C_6H_5, R = $C_6H_4OCH_3$-*p*,
e, Ar = C_6H_4Cl-*p*, R = C_6H_5,
f, Ar = C_6H_4Cl-*p*, R = $C_6H_4CH_3$-*p*,
g, Ar = $C_6H_4OCH_3$-*p*, R = $C_6H_4CH_3$-*p*,
h, Ar = $C_6H_4OCH_3$-*p*, R = $C_6H_5CH_2$,
i, Ar = R = C_6H_4Cl-*p*.

---

[1] A. Mustafa and A. H. E. Harhash, *J. Org. Chem.* **21**, 575 (1956); R. Filler and J. D. Wisman, *Ibid.* **22**, 853 (1957).

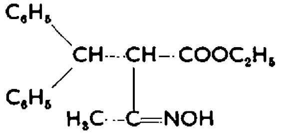
[2] L. Panizzi *Gazz. Chim. Ital.* **76**, 44 (1946).

[3] A. Mustafa and M. M. M. Sallam *J. Org. Chem.* **27**, 2406 (1962).



VI

The reaction of IVa-c with alkyl- and arylmagnesium halides under different conditions reveals that treatment of IVa-c with excess of Grignard reagents by the normal and inverse methods effects the addition of the reagent to the exocyclic double bond with the formation of Va-h. The structure of Va has been proved by synthesis via the reaction of ethyl α-benzhydryl-acetoacetate with hydroxylamine hydrochloride, followed by cyclization of the oxime (VII) with a mixture of acetic and hydrochloric acids. Moreover, it is identical with the product obtained in the Friedel-Crafts reaction (see below). Further evidence for the structure of the products, is the identity of Vd, obtained by the action of *p*-anisyl-magnesium bromide on IVa, and by the action of phenylmagnesium bromide on IVc.



VII

The Grignard reagents do not open the hetero-ring, but addition takes place to the conjugation created by attachment to the exocyclic double bond in the 4-position of a heterocyclic ring having a carbonyl function (IV)*. Whereas the oxazolone ring in 2-phenyl-4-methyl-5(4H)oxazolone[5] and 2-phenyl-4-benzhydryl-5(4H)oxazolone[3] is readily opened by the action of phenylmagnesium bromide, the isoxazolone ring in Va is stable towards the same reagent.

The behaviour of conjugated arylidene derivatives of 3-methylisoxazolin-5-one (IV) in the Friedel Crafts reaction, shows that in the case of IVa-b the reaction with benzene, toluene or chlorobenzene, in the presence of anhydrous aluminium chloride results in the formation of 1,4-addition products (Va,b,e,f,i), this reactivity of the exocyclic double bond being similar to that of I[3,6] towards the same reagent.

The behaviour of the isoxazolone ring in the presence of hydrazines shows that whereas the ring in 3-methylisoxazolin-5-one (VIII) and in 4-arylazo derivatives (IX) is rapidly opened with hydrazine hydrate, followed by immediate cyclization to

---

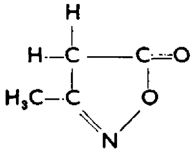
* For similar behaviour with 4-arylidene derivatives of other heterocyclic rings, compare Mustafa and Sallam.[4]

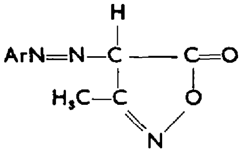
[4] A. Mustafa and M. M. M. Sallam, *J. Org. Chem.* **26**, 1782 (1961).

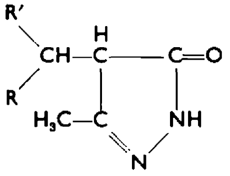
[5] E. Mohr and F. Sroschein, *Ber. Dtsch. Chem. bes.* **42**, 2521 (1909); H. T. Clarkes, Jr. Johnson and R. Robinson, *The Chemistry of Penicillin* p. 738. Princeton University Press, Princeton, N.J. (1949).

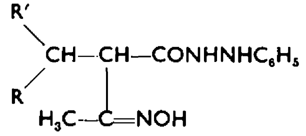
[6] R. Filler and L. M. Hebron, *J. Org. Chem.* **23**, 1815 (1959); R. Filler and Y. S. Rao, *Ibid.* **27**, 2403 (1962).

3-methylpyrazolin-5-one[7] and 4-arylazo-3-methylpyrazolin-5-one[8] respectively; Fusco and Musante[9] have claimed the stability of the isoxazolone ring in 4-arylidene-3-methylisoxazolin-5-one (IV) toward the action of hydrazines. The authors have shown that the arylidene group is eliminated as the corresponding aldehyde hydrazone derivative. Papini and Franco[10] have also reported the stability of the isoxazolone ring in 4-anilinomethylene-, and 4-aldehydo-3-methylisoxazolin-5-one toward the action of phenyl-hydrazine.


VIII

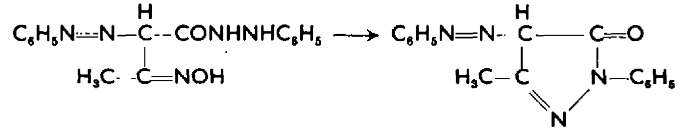

IX

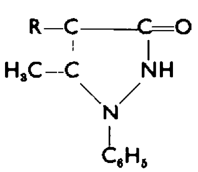


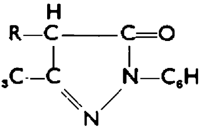


Xa, $R = R' = C_6H_5$,
b, $R = C_2H_5$, $R' = C_6H_5$,
c, $R = C_6H_5$, $R' = C_6H_4OCH_3$-*p*,
d, $R = C_6H_5CH_2$, $R' = C_6H_4OCH_3$-*p*,

XIa, $R = R' = C_6H_5$,
b, $R = C_2H_5$, $R' = C_6H_5$,
c, $R = C_6H_5$, $R' = C_6H_4OCH_3$-*p*,
d, $R = C_6H_5CH_2$, $R' = C_6H_4OCH_3$-*p*,


XII XIII





XIVa, $R = H$,
b, $R = (C_6H_5)_2CH$.

XVa, $R = H$,
b, $R = (C_6H_5)_2CH$.

The behaviour of the hetero-ring in 4-substituted-3-methylisoxazolin-5-ones (V) in the presence of hydrazines has been investigated. In accordance with the findings of Rothenberg,[7] Va, c, d, h are readily converted to the 4-substituted 3-methylpyrazolin-5-ones (Xa-d) by the action of hydrazine hydrate, but with phenylhydrazine, we have obtained a number of intermediate hydrazides (XIa-d). Cyclization of these hydrazides under different experimental conditions leads to different products. When

---

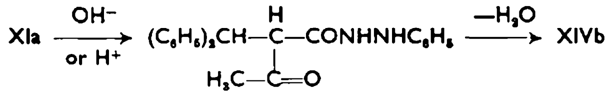
[7] R. V. Rothenberg, *J. Prakt. Chem.* [2] **51**, 59 (1895).

[8] G. Bulow and A. Heeking, *Ber. Dtsch. Chem. bes.* **44**, 468 (1911).

[9] R. Fusco and C. Musante, *Gazz. Chim. Ital.* **67**, 248 (1937).

[10] P. Papini and G. Franco, *Gazz. Chim. Ital.* **81**, 230 (1951).

XIa is treated with boiling acetic acid 4-benzhydryl-3-methylisoxazolin-5-one (Va) is obtained. This is analogous to the ring closure of acetoacetanilide oxime with acetic acid to give 3-methylisoxazolin-5-one (VIII)[11] and in contrast to the ring closure of XII to XIII by the action of acetic acid.[12] Compound XIa undergoes ring closure by the action of alcoholic sodium hydroxide or hydrochloric acid to give 4-benzhydryl-5-methyl-1-phenylpyrazolin-3-one (XIVb). Lecher *et al.*[13] have shown that arylhydrazones of acetoacetic arylhydrazides, when heated with strong aqueous mineral acids, the hydrazone linkage is hydrolysed and the resulting acetoacetic arylhydrazide readily forms 1-aryl-5-methylpyrazolin-3-one (XIVa) by internal ring closure. On the other hand, the action of acetic acid or aqueous sodium hydroxide effects the internal ring closure to 3-methyl-1-phenylpyrazolin-5-one (XVa). The ring closure of arylhydrazones of acetoacetic arylhydrazides to pyrazolin-5-one derivatives, is analogous to the cylization of XII to XIII by the action of alcoholic sodium hydroxide or hydrochloric acid. This reaction constitutes a simple synthesis of compounds of the type XIV. The formation of XIVb on heating XIa with alcoholic sodium hydroxide or with hydrochloric acid can be explained by hydrolysis of the oxime linkage, resulting in the formation of phenylhydrazide of α-benzhydrylacetoacetic acid (XVI). This latter compound presumably loses water with the formation of XIVb. On the other hand, heating XIa with acetic acid effects the cleavage of the phenylhydrazide linkage to give the oxime derivative of α-benzhydrylacetoacetic acid. The latter presumably loses water to give IVa.



$$\mathrm{XIa} \xrightarrow[\text{or } H^+]{OH^-} (C_6H_5)_2CH-\underset{H_3C-C=O}{\overset{H}{C}}-CONHNHC_6H_5 \xrightarrow{-H_2O} \mathrm{XIVb}$$

XVI

Structure Xa has been proposed for the 4-benzhydrylpyrazolone derivative since it is identical with the product obtained by the action of hydrazine hydrate on ethyl α-benzhydryl acetoacetate—a general procedure adopted for the preparation of pyrazolin-5-ones. The formation of Xa is analogous to the preparation of 3-methylpyrazolin-5-one by the action of hydrazine hydrate on VIII.[7]

The structure XIVb is confirmed by its synthesis although in poor yield, according to the general procedure described by Michaelis.[14] Moreover, XIVb, proved not to be identical with the isomeric pyrazolin-5-one derivative (XVb), is readily obtained by the action of phenyl-hydrazine on ethyl α-benzhydrylacetoacetate in acetic acid; XVb is identical with the product obtained by the action of phenylmagnesium bromide on 4-benzylidene-3-methyl-1-phenylpyrazolin-5-one.[15]

The phenylhydrazide (XIa) is now obtained by the action of phenylhydrazine on the oxime derivative of ethyl α-benzhydryl-acetoacetate (VII).

The behaviour of the isoxazolone ring toward nucleophilic reagents is now in progress.

---

[11] L. Knorr and B. Reuter, *Ber. Dtsch. Chem. Ges.* **27**, 1169 (1894).

[12] A. Mustafa, W. Asker, A. F. A. Shalaby, Z. Selim and C. R. Daguer, *J. Org. Chem.* **27**, 4201 (1962).

[13] H. Z. Lecher, R. P. Parker and R. C. Conn, *J. Amer. Chem. Soc.* **66**, 1959 (1944).

[14] A. Michaelis, *Liebig's. Ann.* **338**, 273 (1904).

[15] A. Mustafa, W. Asker, A. F. A. Shalaby, S. A. Khattab and Z. E. Selim, *J. Amer. Chem. Soc.* **81**, 6007 (1959).

EXPERIMENTAL

Action of Grignard reagents on 2-*arylidene*-3-*methylisoxazolin*-5-*ones* (IVa-c)

General procedure. A Grignard solution (prepared from 1·0 g magnesium and the appropriate quantity of the alkyl halide in 100 ml. dry ether) was added to each of IVa–c (2·0 g) in dry ether (100 ml). The reaction mixture was refluxed (steam-bath) for 2 hr, most of the ether evaporated, and then decomposed with dilute (1 : 15) hydrochloric acid. The product was filtered off, washed with ether and crystallized from alcohol. If an oily residue was obtained, it was extracted with ether. The ethereal layer was separated, washed several times with water, and allowed to evaporate slowly. The oily residue solidified by trituration with dil alcohol and was then crystallized from alcohol.

The 4-substituted-3-methylisoxazolin-5-ones (Va-h), listed in Table 1, are all colourless soluble in aqueous sodium hydroxide (10%), and give a yellow colour with conc sulphuric acid. Compound Va was recovered unchanged upon treatment with phenylmagnesium bromide under the same conditions.

An authentic sample of Va was prepared via the oxime derivative of ethyl α-benzhydrylacetoacetate (VII) as follows: A solution of hydroxylamine hydrochloride (0·3 g) in 50% aqueous alcohol (10 ml) was added to ethyl α-benzhydrylacetoacetate[16] (1·0 g) and the mixture boiled for a few min. The crystals of VII (0·25 g), which separated on cooling, were recrystallized from alcohol, m.p. 154° (Found: N, 4·35; $C_{19}H_{21}NO_3$ requires: N, 4·50%).

A suspension of VII (0·5 g) in acetic acid (10 ml) and hydrochloric acid (5 ml) was refluxed for 2 hr, the reaction mixture cooled and poured into ice-cold water. The product (0·4 g) crystallized from alcohol, m.p. 171° and is identical by mixed m.p. with the Grignard product Va.

Reaction of 2-*arylidene*-3-*methylisoxazolin*-5-*ones* (IVa–c) *with aromatic hydrocarbons in presence of aluminium chloride*

The following illustrates the procedure: To a suspension of anhydrous aluminium chloride (3·2 g) in dry thiophene-free benzene (60 ml), which was previously stirred for 1 hr, a solution of 4-benzylidene-3-methylisoxazolin-5-one (IVa; 2·0 g) in dry benzene (75 ml) was added gradually and stirring continued for an additional 3 hr at room temp. The complex was decomposed with dilute (1 : 15) hydrochloric acid (150 ml), the benzene solution separated, dried and evaporated under red. press. The oily residue was triturated with dil alcohol and the product (1·6 g) crystallized from alcohol proved to be identical (m.p. and mixed m.p. and I.R. spectra) with the Grignard product Va.

In a similar manner treatment of IVa with toluene or chloro-benzene and of IVb with benzene or toluene gave products identical with the corresponding Grignard products. Yields were 56, 65, 60 and 58% respectively.

Similarly, the treatment of IVb with chlorobenzene yielded 4-(bis-*p*-chlorophenylmethyl)-3-methylisoxazolin-5-one (Vi) which was crystallized from alcohol as colourless prisms, m.p. 168° (Found: C, 61·40; H, 4·13; N, 4·24; Cl, 20·84. $C_{17}H_{13}NO_2Cl_2$ requires: C, 61·08; H, 3·89; N, 4·19; Cl, 21·26%),

Action of hydrazine hydrate on Va, c, d, *and* h

A suspension of each of Va, c, d and h (1·0 g) in hydrazine hydrate (2·0 ml) was heated on a water-bath for 2 hr, the reaction mixture cooled, triturated with dil alcohol and the product crystallized from alcohol.

The 4-substituted-3-methylpyrazolin-5-ones (Xa-d), listed in Table 2, are colourless, soluble in aqueous sodium hydroxide (10%) and give a yellow colour with conc sulphuric acid.

Xa was found to be identical with an authentic sample obtained by the action of hydrazine hydrate on ethyl α-benzhydrylacetoacetate.

Action of phenylhydrazine on Va, c, d, *and* h

To each of Va, c, d, and h (1·0 g) phenylhydrazine (1·0 ml) was added, and the mixtures were heated on a water-bath for 2 hr. The solids, obtained upon dilution with alcohol, were crystallized from the proper solvent (c.f. Table 3).

The phenylhydrazines (XIa-d), listed in Table 3 are colourless, insoluble in aqueous sodium hydroxide (10%) and give a yellow colour with conc sulphuric acid.

---

[16] G. G. Henderson and M. A. Parker, *J. Chem. Soc.* **71**, 676 (1897).

TABLE 1.—GRIGNARD PRODUCTS (V) FROM 2-ARYLIDENE-3-METHYLISOXAZOLIN-5-ONES (IV)

Isoxazolin-5-one derivative.	Grignard reagent, R=	Product	m.p.[a,b]	Yield %	Formula	Carbon, % Calc.	Carbon, % Found	Hydrogen, % Calc.	Hydrogen, % Found	Nitrogen %, Calc.	Nitrogen %, Found
IVa	phenyl	Va	171°	82	$C_{18}H_{15}NO_2$	76·98	76·74	5·66	5·70	5·28	5·06
IVa	*p*-totyl	Vb	130°	79	$C_{18}H_{17}NO_2$	77·42	77·15	6·09	6·12	5·02	5·33
IVa	ethyl	Vc	106°	75	$C_{13}H_{15}NO_2$	71·89	71·85	6·91	6·96	6·45	6·18
IVa	*p*-anisyl	Vd	168°	73	$C_{18}H_{17}NO_3$	73·22	72·94	5·76	5·54	4·75	5·01
IVb	phenyl	Ve	148°	83	$C_{17}H_{14}NO_2Cl$[c]	68·11	68·29	4·67	4·63	4·67	4·59
IVb	*p*-tolyl	Vf	165°	80	$C_{18}H_{16}NO_2Cl$[d]	68·90	68·91	5·10	5·15	4·47	4·85
IVc	phenyl	vd	168°	78	$C_{18}H_{17}NO_3$						
IVc	*p*-tolyl	Vg	144°	76	$C_{19}H_{19}NO_3$	73·79	73·81	6·15	6·24	4·53	4·77
IVc	benzyl	Vh	124°	71	$C_{19}H_{19}NO_3$	73·79	73·69	6·15	6·22	4·53	4·64

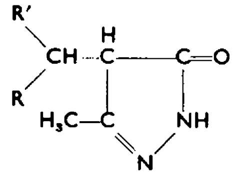
[a] All melting points are uncorrected.

[b] All products melt with decomposition.

[c] Cl: Calc.: 11·85, Found: 11·39.

[d] Cl: Calc.: 11·32, Found: 11·21.

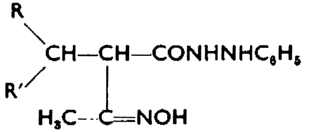
TABLE 2.—4-SUBSTITUTED 3-METHYLPYRAZOLIN-5-ONES (X)



	R	R'	M.p.[a]	Yield, %	Formula	Carbon, % Calc.	Carbon, % Found	Hydrogen, % Calc.	Hydrogen, % Found	Nitrogen, % Calc.	Nitrogen, % Found
Xa	C_6H_5	C_6H_5	218°	65	$C_{17}H_{16}N_2O$	77·27	76·94	6·06	6·17	10·61	11·04
Xb	C_2H_5	C_6H_5	195°	59	$C_{13}H_{16}N_2O$	72·22	72·02	7·41	7·58	12·96	13·17
Xc	C_6H_5	$C_6H_4OCH_3$-*p*	226°	63	$C_{18}H_{18}N_2O_2$	73·47	73·68	6·12	6·49	9·52	9·49
Xd	$C_6H_5CH_2$	$C_6H_4OCH_3$-*p*	213°	67	$C_{19}H_{20}N_2O_2$	74·03	73·84	6·49	6·61	9·09	9·34

[a] All m.p. are uncorrected.

TABLE 3.—OXIMES OF α-SUBSTITUTED ACETOACETIC PHENYLHYDRAZIDES (IX)



	R=	R′=	M.p.[a]	Yield, %	Formula	Carbon, % Calc.	Carbon, % Found	Hydrogen, % Calc.	Hydrogen, % Found	Nitrogen, % Calc.	Nitrogen, % Found
XIa	C_6H_5	C_6H_5	220°	58	$C_{23}H_{23}N_3O_2$	73·99	73·64	6·17	6·38	11·18	11·29
XIb	C_2H_5	C_6H_5	181°	55	$C_{19}H_{23}N_3O_2$	70·15	70·41	7·08	6·92	12·92	12·57
XIc	C_6H_5	$C_6H_4OCH_3$-*p*	193°	62	$C_{24}H_{25}N_3O_3$	71·46	70·98	6·20	6·26	10·42	10·40
XId	$C_6H_5CH_2$	$C_6H_4OCH_3$-*p*	198°	61	$C_{25}H_{27}N_3O_3$	71·94	72·14	6·47	6·84	10·07	9·65

[a] All m.p. are uncorrected.

XIa was found to be identical (m.p. and mixed m.p.) with an authentic sample prepared in 35% yield by warming a mixture of the oxime derivative of ethyl α-benzhydrylacetoacetate (VII) (0·5 g) and phenylhydrazine (1·0 ml) on a water-bath for 6 hr and working up the reaction mixture as above.

Behaviour of XIa

(a) *Acetic acid.* A suspension of XIa (0·5 g) in glacial acetic acid was refluxed for 1 hr and the mixture poured into ice-cold water yielding a solid (0·4 g) which crystallized from alcohol, m.p. 171° alone or mixed with Va.

(b) *Sodium hydroxide.* A mixture of XIa (1·0 g) 10% aqueous sodium hydroxide (20 ml) and alcohol (20 ml) was refluxed for 2 hr, the resulting solution cooled, poured into ice-cold water and acidified with hydrochloric acid. The product (0·7 g) was crystallized from alcohol as colourless needles, m.p. 209° (Found: C, 81·00; H, 5·69; N, 8·48. $C_{23}H_{20}N_2O$ requires: C, 81·18: H, 5·88; N, 8·24%).

4-Benzhydryl-5-methyl-1-phenylpyrazolin-3-one (XIVb) is colourless, insoluble in aqueous sodium hydroxide (10%) and gives a yellow colour with conc sulphuric acid.

XIVb was found to be identical with an authentic sample prepared according to Michaelis[14] as follows: A mixture of ethyl α-benzhydrylacetoacetate (1·5 g) β-acetylphenylhydrazine (0·8 g), phosphorous trichloride (0·9 g) was heated on a water-bath for 2 hr, cooled, and poured into ice-cold water. The solid (0·7 g) was collected and repeatedly crystallized from alcohol, m.p. 209°.

(c) *Hydrochloric acid.* A suspension of XIa (0·8 g) in a mixture of conc hydrochloric acid (20 ml) and alcohol (20 ml) was refluxed for 2 hr. The reaction mixture was cooled, poured into ice-cold water and the product (0·6 g) crystallized from alcohol, and identified as XIVb by m.p. and mixed m.p.

3-*Methyl-4-phenylazo*-1-*phenylpyrazolin*-5-*one* (XIII)

This compound was obtained upon treatment of XII with either sodium hydroxide or hydrochloric acid in a similar manner to the treatment of XIa with the same reagents as described above. Yields were 76 and 80% respectively. Identifications was carried out with an authentic specimen.[12]

4-*Benzhydryl*-3-*methyl*-1-*phenylpyrazolin*-5-*one* (XVb)

A mixture of ethyl α-benzhydrylacetoacetate (1·5 g) phenylhydrazine (1·0 ml) and acetic acid (5·0 ml) was heated on a water-bath for 15 min, the reaction mixture poured into ice-cold water and the product (1·6 g) crystallized from alcohol, m.p. 220°, alone or mixed with an authentic specimen.[15]