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REACTIONS WITH 1(2H)-PHTHALAZINONES, 4,5-DIHYDRO-3(2H)-PYRIDAZINONES AND 3-PYRAZOLIN-5-ONES

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Abstract—The condensation of 1(2H)-phthalazinones (Ia–c), 4,5-dihydro-6-phenyl-3(2H)-pyridazinone (IIIa), and 4-arylidene-4,5-dihydro-6-phenylpyridazinones (IVa–b) with secondary amines and formaldehyde yields the corresponding N-Mannich-bases (Id, IIIc–d, and IVi–j, respectively). Similarly, reaction with acrylonitrile, affords the cyanoethylated products (Ig, IIIf, and IVk–l, respectively). The Mannich-bases (Id) are also obtained by reaction of the appropriate amines with the corresponding chloromethyl- (If), or hydroxymethylphthalazinone derivatives (Ie); and by treatment of the hydroxymethyl derivative of IIIa with the same reagents. In the presence of ethylamine, the condensation of Ia–c with formaldehyde yields the corresponding bis-derivatives (II).

The reaction of 3-methyl-2-phenyl-3-pyrazolin-5-one (Va) with formaldehyde and piperidine or morpholine involves the hydrogen atom on C_4 with formation of the Mannich-bases (Vd–e). In addition, the synthesis of some of the corresponding bis-derivatives (VI) are reported. The IR spectra of the reaction products are discussed. Interaction of Vd with aromatic thiols leads to the formation of 4-arylthiomethyl-3-methyl-2-phenyl-3-pyrozolin-5-ones (IVf–i). The latter compounds react with ethereal diazomethane yielding products believed to have structures similar to VII.

Treatment of 2-N-piperidinomethyl-4-phenyl-1(2H)-phthalazinone (cf. Id), and 2-N-piperidinomethyl-6-phenyl-4,5-dihydro-3(2H)-pyridazinone (IIIe) with phenylmagnesium bromide, followed by hydrolysis, gives 1,4-diphenylphthalazine and 3,6-diphenylpyridazine (VIII), respectively. The latter has also been obtained by the action of the same reagent on IIIa and/or 6-phenyl-3(2H)-pyridazinone.

THE condensation of aldehydes and amines with compounds possessing an active hydrogen atom is a convenient method of introducing aminomethyl groups.[1] In heterocyclic compounds, three types of active hydrogen atoms may be involved: (a) those directly attached to the nucleus,[2] (b) those attached to the α-carbon of an alkyl group attached to the ring;[3] and (c) those attached to side-chains where the activation is provided by some groups other than the ring.[4]

In this investigation a series of compounds of type (a) have been prepared for the purpose of studying the reaction in the heterocyclic nitrogen series, and also to determine the most active hydrogen in various ring systems. Treatment of methalonic

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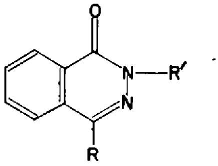
[1] For a review, see F. F. Blicke, *The Mannich reaction* Vol. I; Chap. 10, of *Organic Reactions* (Edited by R. Adams) John Wiley, N.Y. (1942).

[2] [a]C. Mannich and W. Krosche, *Arch. Pharm.* **250**, 647 (1912); [b]H. Kuhn and O. Stein, *Ber. Dtsch. Chem. Ges.* **70**, 567 (1937); [c]G. Bachman and L. V. Heisy, *J. Amer. Chem. Soc.* **68**, 2496 (1946); [d]N. F. Alberston, *Ibid.* **70**, 669 (1948); [e]H. Hellman and I. Loschmann, *Chem. Ber.* **89**, 594 (1956); [f]J. N. Coker and M. Fields, *J. Org. Chem.* **27**, 2226 (1962).

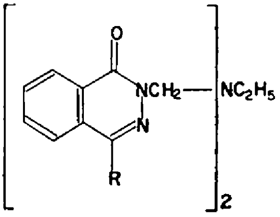
[3] H. Héou-Féou, *C.R. Acad. Sci., Paris*, **192**, 1242 (1931); R. Pfleger and G. Maskert, *Chem. Ber.* **90**, 1494 (1957); W. O. Kermark and W. Muir, *J. Chem. Soc.* 3089 (1931); M. S. Linder and P. E. Spoerri, *J. Amer. Chem. Soc.* **74**, 1517 (1952).

[4] G. A. Levvy and H. B. Nisbet, *J. Chem. Soc.* 1053 (1938).

solutions of 1(2H)-phthalazinones (Ia–c) with secondary amines and aqueous formaldehyde yields crystalline N-Mannich-bases (Id; cf. Table 2). The Mannich-reaction with Ia–c, in the presence of ethylamine, under similar experimental conditions, yields the bis-derivatives (II; cf. Table 2).[5] Elemental analysis of the derivatives indicates that the substituted dialkylaminomethyl group attaches itself to the ring nitrogen with the formation of Id.



I



II

Ia, R' = R = H
b, R' = H; R = CH_3
c, R' = H, R = C_6H_5
d, R' = Disubstituted aminomethyl
e, R' = CH_2OH
f, R' = CH_2Cl
g, R' = CH_2CH_2CN
h, R' = CH_2CH_2COOH

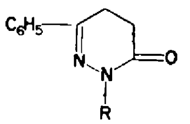
The possible formation of N-Mannich-bases (Id) by condensation of the amine with methylol[1] formed as an intermediate has now been examined. The N-hydroxymethyl derivatives (Ie, R = H, CH_3 and C_6H_5), obtained via the reaction of Ia–c with formaldehyde, condense with piperidine, in the presence of methanol, giving good yields of the expected products. This is consistent with the reported observation that 1-hydroxymethyl-2-dialkylaminomethylbenzimidazolones give 1,3-bis(dialkylaminomethyl)benzimidazolones upon treatment with an excess of the dialkylamine,[6] but is not in keeping with the stability of the 4-hydroxymethyl derivative of antipyrine towards dimethylamine.[7] It is therefore, not possible to claim with certainty that the methylol formation is the initial step in the Mannich-reaction. Treatment of the N-hydroxymethyl derivative (Ie, R = C_6H_5) with piperidine in absence of a solvent effects the elimination of the hydroxymethyl group with the formation of Ic.

In favour of the proposed structure for the N-Mannich-bases, Id may be synthesized independently by treatment of the appropriate amine with the chloromethyl derivatives (If, R = CH_3, C_6H_5), now obtained by the action of phosphorus oxychloride on Ie.

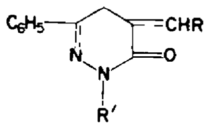
3(2H)-Pyridazinones undergo the Mannich-reaction to yield N-dialkylaminomethyl-3(2H)-pyridazinones.[2e] The condensation of 4,5-dihydro-3-(2H)-pyridazinones with amines and formaldehyde does not appear to have been investigated. Thus in the reaction of 4,5-dihydro-6-phenyl-3(2H)-pyridazinone (IIIa) with the appropriate secondary amine and formaldehyde in the presence of methanol, the substituted dialkylaminomethyl group attaches itself to the ring nitrogen with the formation of IIIc–d. The structure assigned to these products is based on the reactivity

[5] cf. H. W. Heine, M. B. Winstead and R. P. Blair, *J. Amer. Chem. Soc.* **78**, 672 (1956).
[6] H. Zinner and B. Spangenberg, *Chem. Ber.* **91**, 1432 (1958).
[7] K. Bodendorf and G. Koralewski, *Arch. Pharm.* **271**, 101 (1933).

of the —NH— group in 3(2H)-pyridazinones[2e] and 3,5-dimethylpyrazole,[2c] and supported by the stability of IIIb towards secondary amines and formaldehyde under similar conditions. Similarly, 4-arylidene-4,5-dihydro-6-phenyl-3(2H)-pyridazinones (IVa–b; cf. also the possible tautomeric forms), obtained by the interaction of IIIa with the appropriate aldehyde in the presence of sodium ethoxide,[8] condense with piperidine and formaldehyde to yield the N-Mannich-bases (IVi–j). The structures proposed are supported by the fact that IVe–f or tautomeric forms (obtained by the condensation of IIIb with appropriate aldehydes) does not react with secondary amines and formaldehyde under similar conditions.



IIIa, $R = H$
b, $R = C_6H_5$
c, $R = CH_2N$ H
d, $R = CH_2N$ H O
e, $R = CH_2OH$
f, $R = CH_2CH_2CN$



IVa, $R' = H$, $R = C_6H_5$
b, $R' = H$, $R = C_6H_4NO_2$—m
c, $R' = H$, $R = C_6H_4Cl$—p
d, $R' = H$, $R = C_6H_3{:}O_2CH_2$—3:4
e, $R' = R = C_6H_5$
f, $R' = C_6H_5$, $R = C_6H_4NO_2$—m
g, $R' = C_6H_5$, $R = C_6H_4Cl$ - p
h, $R' = C_6H_5$, $R = C_6H_4OCH_3$—p
i, $R' = CH_2N$ H, $R = C_6H_5$
j, $R' = CH_2N$ H, $R = C_6H_4NO_2$—m
k, $R' = CH_2CH_2CN$, $R = C_6H_5$
l, $R' = CH_2CH_2CN$, $R' = C_6H_4NO_2$—m

Whereas, 6-methyl-3(2H)-pyridazinone upon treatment with secondary amines and formaldehyde yields the corresponding 2-hydroxymethyl derivatives,[9] IIIa yields the corresponding N-Mannich-bases (IIIc–d). Furthermore, treatment of IIIe, (obtained by the action of formaldehyde on IIIa) with piperidine in the presence of methanol, results in the formation of the Mannich-base (IIIc).

It is evident that the reaction of antipyrine[2a] and of isoantipyrine[10] with formaldehyde and dialkylamines involves the hydrogen atom on carbon 4. We now have found that 3-methyl-2-phenyl-3-pyrazolin-5-one (Va) in methanol condenses readily with formaldehyde in the presence of piperidine and/or morpholine to give the Mannich-bases (Vd–e). When primary amines, namely ethylamine, aniline, *o*-, and *p*-toluidines are used, the bis-derivatives (VI) are obtained.[5] The structure of the products is again based on the activity of the hydrogen atom on carbon 4 in Va toward substitution reactions.[11] It was found that Vd–e are stable toward the action of amines and thiols, thus favouring the attachment of the disubstituted aminomethyl group to the pyrazolone nucleus rather than the ring nitrogen since the former is not likely to be removed by the reagents used.

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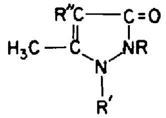
[8] cf. A. Mustafa, S. A. Khattab and W. Asker, *Canad. J. Chem.* **41**, (7), 1813 (1963).

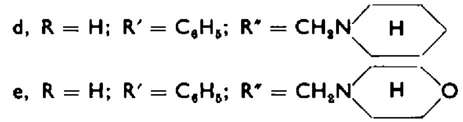
[9] H. Gregory, J. Hills and L. F. Wiggins, *J. Chem. Soc.* 1248 (1949).

[10] C. Mannich and B. Kather, *Arch. Pharm.* **257**, 18 (1919).

[11] A. Michaelis, *Liebig's Ann.* **338**, 267 (1904); P. Kotelmann, *Ibid.* **350**, 267 (1906).

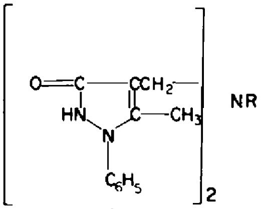


Va, $R = R'' = H$; $R' = C_6H_5$
b, $R = C_6H_5$; $R' = CH_3$; $R'' = H$
c, $R = CH_3$; $R' = C_6H_5$; $R'' = H$



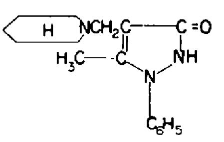
d, $R = H$; $R' = C_6H_5$; $R'' = CH_2N$ H
e, $R = H$; $R' = C_6H_5$; $R'' = CH_2N$ H O

f, $R = H$; $R' = C_6H_5$; $R'' = CH_2SC_6H_5$
g, $R = H$; $R' = C_6H_5$; $R'' = CH_2SC_6H_4CH_3$—o
h, $R = H$; $R' = C_6H_5$; $R'' = CH_2SC_6H_4CH_3$—m
i, $R = H$; $R' = C_6H_5$; $R'' = CH_2SC_6H_4CH_3$—p

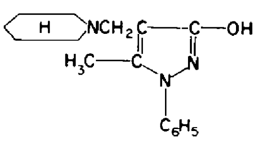


VI

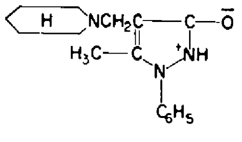
The IR absorption spectrum of Vd shows broad absorption at 2800–2600 cm^{-1} and at 1610–1620 cm^{-1}. The absence of a normal —NH— or —OH band may be attributed to the presence of a strongly bonded hydrogen system[12] (cf. the possible forms A–C). The broad absorption at 1610–1620 cm^{-1} is in support of a structure approximating (C) for the Mannich-base. Although it is known[13] that the $C{=}\underset{|}{N^{+}}H$ group absorption appears at 1660–1680 cm^{-1}; the resulting shift to the longer wavelength may be accounted for by the zwitterion.[14] The amidocarbonyl group, the double bond character of which has been reduced by the dipolar structure (C) should also be at 1600–1620 cm^{-1} and thus accounts for the broadness of the absorption band in this area. The strong absorption in the infrared at 2800–2600 cm^{-1} is associated with acid salts or zwitterion type compounds.[15] Thus, the IR data, which has been



A



B



C

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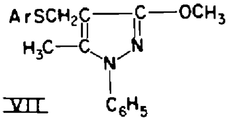
[12] cf. The IR spectra of hydroxypyrazoles: S. Refn, *Spectrochem. Acta* **17**, 40 (1961).
[13] N. J. Leonard and V. W. Gash, *J. Amer. Chem. Soc.* **76**, 2781 (1954).
[14] G. De Stevens, A. Halamandaras, P. Wenk and L. Dorfman, *J. Amer. Chem. Soc.* **81**, 6292 (1959).
[15] B. Witkop, *J. Amer. Chem. Soc.* **78**, 2873 (1956).

advantageously used in the tetrahydroindazolone series,[14] may be applied to the structural problems of Vd–e. Furthermore, had the substituted dialkylaminomethyl group attached itself to the nitrogen, the resulting Mannich-bases would be structurally related to antipyrine (Vb) and/or isoantipyrine (Vc) and would show a cyclic amido band in their IR spectra. The presence of very strong cyclic amido band at 1665 cm^{-1} and at 1690 cm^{-1} in the case of Vb[14] and Vc, and the absence of such a band in Vd is in favour of the predominant amide form in Vb and Vc and the dipolar structure (C) in Vd. This conclusion is further supported by the identity of the IR spectra of Vd and 3,4-dimethyl-2-phenyl-3-pyrazolin-5-one.

Interaction of 3-methyl-2-phenyl-4-N-piperidinomethyl-3-pyrazolin-5-one (Vd) with aromatic thiols at 150°[16] yields the corresponding 4-arylthiomethyl-3-methyl-2-phenyl-3-pyrazolin-5-ones (Vf–i) in good yield. Similarly, VI ($R = C_6H_5$) reacts with thiophenol to yield Vf, the IR spectrum of which is identical with that of Vd.

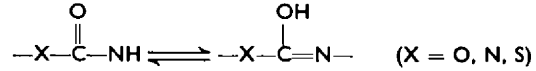
The structures proposed for the arylthiomethyl derivatives (Vf–i) and the Mannich-bases (Vd–e), are supported by the reaction of Vf–i with ethereal diazomethane yielding methylated products (VII), thus proving the availability of an active hydrogen. Alkylation of Vf–i may yield either the O-alkyl or the N-alkyl derivatives (cf. the tautomeric forms). Evidence in favour of the O-methyl structure was obtained by a comparison of the IR spectra of the methylated products with the IR spectrum of isoantipyrine (Vc), which is structurally related to the N-methylated derivatives.



VII

The IR spectra of the methylated products reveal a band of medium strength at 1620 cm^{-1} ($C = N$ vibration) and do not exhibit absorption bands at 1689–1700 cm^{-1} (cyclic amido vibration). On the other hand Vc does show a strong cyclic amido band at 1690 cm^{-1}. Therefore, only a careful reexamination of this problem can ascertain whether diazomethane has, in fact, produced the O-methyl derivatives.

Cyanoethylation of heterocyclic nitrogen systems has recently received much attention* but considerable confusion exists regarding the structure of the addition products of acrylonitrile to the tautomeric compounds present in a large number of heterocyclic nitrogen systems.



$$—X—\overset{\overset{O}{\|}}{C}—NH \rightleftharpoons —X—\overset{\overset{OH}{|}}{C}{=}N— \quad (X = O, N, S)$$

Cyanoethylation of 1(2H)-phthalazinones (Ia–c), 4,5-dihydro-6-phenyl-3(2H)-pyridazinone (IIIa) and 4-arylidene-4,5-dihydro-6-phenyl-3(2H)-pyridazinones (IVa–b) reveals that the ring nitrogen[17] is involved rather than on the hydroxyl oxygen with

*see Ref 17.

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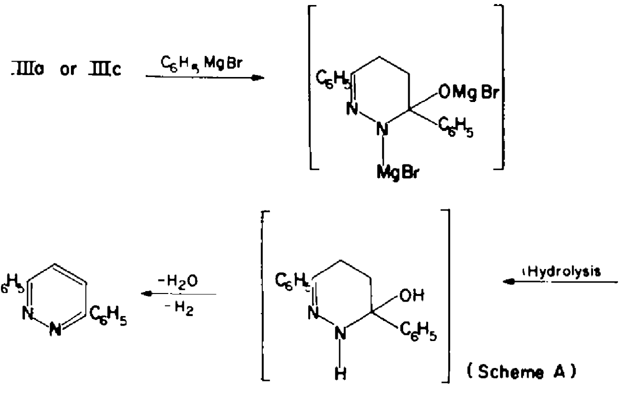
[16] F. Poppelsdorf and S. J. Holt, *J. Chem. Soc.* 1124 (1954).

[17] Cyanoethylation has been reported on the heterocyclic nitrogen atom in 5(6)-nitrobenzimidazole (A. M. Efros, *Zh. Obschcheĭ Kim.* **30**, 3565 (1960); *Chem. Abstr.* **55**, 18712 (1961); 4-hydroxy-7-methylpteridine (W. V. Curran and R. B. Angier, *J. Org. Chem.* **26**, 2364 (1961); 4,5-dihydro-6-hydroxy-3(2H)-pyridazinone (H. Feuer, G. B. Silverman, H. P. Angstadt and A. R. Fauke, *Ibid.* **27**, 2081 (1962)); 2-mercaptobenzothiazoles (J. M. Sprague and A. H. Land, *Heterocyclic Compounds* (Edited by R. C. Elderfield) Vol. 5; p. 566. J. Wiley, N.Y. (1957); and 2-thiazoline-2-thiol (R. J. Gaul, W. J. Fremuth and M. N. O'Connor, *J. Org. Chem.* **26**, 5106 (1961).

the formation of Ig (R = H, CH_3, C_6H_5), IIIf and IVk–l respectively. The chemical behaviour and IR spectra of these products are compatible with the proposed structures. The compounds are insoluble in dilute acids; mild hydrolysis produces the corresponding carboxylic acids (Ih) in good yield and the IR spectrum of Ig (R = C_6H_5) reveals carbonyl absorption maximum which agrees with that shown by the parent six-membered ring compound.

Recently it was shown[18] that 1,4-diphenylphthalazine is readily obtained by addition of phenylmagnesium bromide to 1(2H)-phthalazinone, 4-phenyl-, and 4-phenyl-2-acetyl-1(2H)-phthalazinones as well as 1(2H)-phthalazinthione. It is now reported that 1,4-diphenylphthalazine is readily produced by treatment of 2-N-piperidinomethyl-4-phenyl-1(2H)-phthalazinone (Id, R′ = N-piperidinomethyl) with phenylmagnesium bromide. This elimination of the piperidinomethyl group by the Grignard reagent is analogous to the elimination of the acetyl group from 2-acetyl-4-phenyl-1(2H)-phthalazinone,[18] N-acetylhydrazone of benzaldehyde,[19] and 1-benzoyltriazole[20] by the same reagent.

Similarly, 2-N-piperidinomethyl-4,5-dihydro-6-phenyl-3(2H)-pyridazinone (IIIc) reacts with phenylmagnesium bromide to yield 3,6-diphenylpyridazine (VIII) which is also produced by the action of the same reagent on 4,5-dihydro-6-phenyl-3(2H)-pyridazinone (IIIa) and 6-phenyl-3(2H)-pyridazinone. It is believed that the formation of VIII proceeds via the sequence of reactions indicated in scheme A. 1,2- Addition of phenylmagnesium bromide to the carbonyl group in IIIa and IIIc is analogous to the addition of the same reagent to the carbonyl group in N-methylisocarbostyrils to give 1-substituted N-methylisoquinolinium compounds.[21] The ease with which the tetrahydro derivatives of type D lose hydrogen may be attributed to autoxidation.[22] The structure of VIII was confirmed by analyses and its identity with an authentic specimen of 3,6-diphenylpyridazine.



(Scheme A)

D

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[18] A. Mustafa, A. H. Harhash and A. A. S. Saleh, *J. Amer. Chem. Soc.* **82**, 2735 (1960).

[19] P. Grammaticakis, *C.R. Acad. Sci., Paris* **208**, 1910 (1939).

[20] A. Mustafa, W. Asker and O. H. Hishmat, *J. Amer. Chem. Soc.* **77**, 5127 (1955).

[21] H. Decker and R. Pschorr, *Ber. Dtsch. Chim. Ges.* **37**, 3386 (1904); H. Erlenmeyer, H. Baumann and E. Sorkin, *Helv. Chim. Acta* **31**, 1978 (1948).

[22] R. C. Elderfield, *Heterocyclic Compounds* Vol. 6, p. 113 J. Wiley, New York, N.Y. (1957).

EXPERIMENTAL

The IR spectra were measured in nujol solution using a Perkin–Elmer model 137B.

4-Arylidene derivatives of 6-phenyl-(IIIa) *and 2,6-diphenyl-4,5-dihydro-*3(2H)*-pyridazinone* (IIIb)

General procedure. To a solution of IIIa or IIIb (0·01 mole) and the appropriate aldehyde (0·015 mole) in absolute ethanol (50 ml), sodium ethylate solution (prepared by dissolving 0·23 g Na in 20 ml ethanol) was added and the reaction mixture left overnight at room temp. The solid obtained upon dilution of the reaction mixture with water was filtered off and crystallized (cf. Table 1).

The arylidene derivatives (IVa–h), listed in Table 1 are almost colourless, they are insoluble in NaOH aq., and give a yellow colour with conc. H_2SO_4.

Mannich-reaction with 1(2H)*-phthalazinones* (Ia–c), *4,5-dihydro-6-phenyl-*3(2H)*-pyridazinones* (IIIa, IVa–b) *and 3-methyl-2-phenyl-3-pyrazolin-5-one* (Va)

General procedure. To a suspension of the compound (0·01 mole) and the appropriate amine (0·02 mole) in methanol (cf. Table 2), aqueous formaldehyde (35%, 2·5 ml) was added. The reaction mixture was heated on a water-bath to ensure complete dissolution, kept overnight at room temp, diluted with water and the resulting solid product, crystallized (cf. Table 2). In cases where no solid was obtained upon dilution with water, the product was isolated by extraction with benzene and evaporation of the benzene layer.

The reaction was also carried out by mixing the appropriate amine, formaldehyde and methanol, adding the corresponding compound after 15 min, and then proceeding as outlined. The yields of the Mannich-bases obtained in each case were almost the same as those reported in Table 2.

The Mannich-bases (Id, II, IIIc–d, IVi–j, Vd–e, and VI), listed in Table 2 are all colourless and give no colour with conc. H_2SO_4.

4,5-Dihydro-2,6-diphenyl-3(2H)-pyridazinone (IIIb) and its 4-arylidene derivatives (IVe–h) were recovered unchanged when treated with piperidine and formaldehyde as described.

2-Hydroxymethyl derivatives of 1(2H)*-phthalazinones and 4,5-dihydro-6-phenyl-*3(2H)*-pyridazinone*

General procedure. A mixture of the appropriate compound (1·0 g), aqueous formaldehyde (35%, 10 ml) and water (50 ml) (in the case of Ia and IIIa) or methanol (50 ml) (in the case of Ib–c) was refluxed 3 hr, cooled and the crystals which separated recrystallized.

2-Hydroxymethyl-1(2H)-phthalazinone (Ie, R = H), crystallized from benzene–pet. ether as colourless needles, m.p. 125° (dec), yield 0·95 g. (Found: C, 61·17; H, 4·46; N, 15·62. $C_9H_8O_2N_2$ requires: C, 61·36; H, 4·55; N, 15·91%).

2-Hydroxymethyl-4-methyl-1(2H)-phthalazinone (Ie, R = CH_3) formed colourless needles from benzene, m.p. 177° (dec), yield 0·93 g. (Found: C, 63·01; H, 5·03; N, 14·66. $C_{10}H_{10}O_2N_2$ requires; C, 63·16; H, 5·26; N, 14·74%).

2-Hydroxymethyl-4-phenyl-1(2H)-phthalazinone (Ie, R = C_6H_5) gave colourless needles from benzene, m.p. 182° (dec), yield 0·90 g. (Found: C, 71·32; H, 4·71; N, 11·53. $C_{15}H_{12}O_2N_2$ requires: C, 71·43; H, 4·76; N, 11·11%).

2-Hydroxymethyl-4,5-dihydro-6-phenyl-3(2H)-pyridazinone (IIIe), crystallized from pet. ether (b.p. 60–80°) as colourless needles, m.p. 122° (dec), yield 0·9 g. (Found: C, 64·17; H, 5·82. $C_{11}H_{12}O_2N_2$ requires: C, 64·71; H, 5·88%).

*2-Chloromethyl-*1(2H)*-phthalazinones* (If). A mixture of the appropriate 2-hydroxymethyl-1(2H)-phthalazinone (Ie, R = CH_3, C_6H_5; 1·0 g) and phosphorus oxychloride (20 ml) was refluxed 2 hr and cooled. The reaction mixture was poured gradually into ice-cold water and after decomposition of the oxychloride was extracted with benzene. The solid, obtained by evaporation of the benzene, was crystallized from benzene–pet. ether.

2-Chloromethyl-4-methyl-1(2H)-phthalazinone (If, R = CH_3) formed colourless needles, m.p. 173°, yield 0·95 g. (Found: C, 57·34; H, 4·11; N, 13·13; Cl, 16·92. $C_{10}H_9ON_2Cl$ requires: C. 57·55; H, 4·28; N, 13·43; Cl, 17·03%).

2-Chloromethyl-4-phenyl-1(2H)-phthalazinone (If, R = C_6H_5) formed colourless needles, m.p. 127°, yield 1·0 g. (Found: C, 66·63; H, 4·39; N, 10·29; Cl, 12·83. $C_{15}H_{11}ON_2Cl$ requires: C, 66·54; H, 4·07; N, 10·35; Cl, 13·12%).

The 2-chloromethyl derivatives (If) are insoluble in NaOH aq. and give a brown colour with conc. H_2SO_4.

TABLE 1. 4-ARYLIDENE-6-PHENYL-3(2H)-PYRIDAZINONES

Arylidene derivative	Solvent of crystallization[a]	M.p.[b]	Yield, %	Formula	Carbon. %		Hydrogen, %		Nitrogen, %	
					Found	Calc.	Found	Calc.	Found	Calc.
IVa	A	177°	74	$C_{17}H_{14}ON_2$	77·54	77·84	5·21	5·38	10·58	10·68
IVb	B	189°	80	$C_{17}H_{13}O_3N_3$	66·23	66·44	4·11	4·26	13·47	13·68
IVc	A	169°	76	$C_{17}H_{13}ON_2Cl$[d]					9·21	9·44
IVd	C	182°	71	$C_{18}H_{14}O_3N_2$					8·96	9·15
IVe	A	123°	73	$C_{23}H_{18}ON_2$	82·04	81·63	5·50	5·36	7·81	8·28
IVf	B	224°	79	$C_{23}H_{17}O_3N_3$					10·72	10·96
IVg	B	140°	75	$C_{23}H_{17}ON_2Cl$[e]	74·17	74·09	4·80	4·56	7·35	7·52
IVh	A	107°	71	$C_{24}H_{20}O_2N_2$	77·94	78·24	5·64	5·47	7·34	7·60

[a] A, Alcohol; B, Acetone; C, Alcohol-water mixture.

[b] All m.p.s are uncorrected.

[c] Not depressed when mixed with an authentic sample prepared after Mustafa and coworkers, ref. 8.

[d] Cl, found: 11·78; calc. 11·97%.

[e] Cl, found: 9·66; calc. 9·53%

TABLE 2

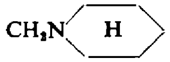
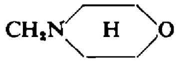
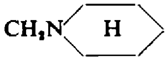
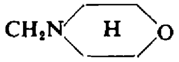
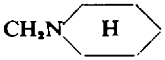
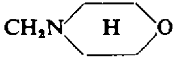
		Volume of methanol, ml.	Solvent of crystallization[a]	M.p.[b]	Yield,%	Formula	Carbon, %		Hydrogen, %		Nitrogen, %	
							Found	Calc.	Found	Calc.	Found	Calc.
				2-Aminomethyl Derivatives of 1(2H)-Phthalazinones								
R =	Compound (Id) R′ =											
H	$CH_2N(CH_3)_2$	40	E	125°	69	$C_{11}H_{13}ON_3$	64·84	65·00	6·31	6·45	20·47	20·68
H	$CH_2N(C_2H_5)(C_6H_5)$	50	A	108°	65	$C_{17}H_{17}ON_3$	73·12	73·09	5·85	6·13	14·72	15·04
H		50	D	81°	63	$C_{14}H_{17}ON_3$	69·05	69·11	7·02	7·00	17·01	17·28
H		40	E	136°	71	$C_{13}H_{15}O_2N_3$	63·93	63·66	6·08	6·16	16·78	17·13
CH_3	$CH_2N(CH_3)_2$	20	C	172°	72	$C_{12}H_{15}ON_3$	66·11	66·34	6·77	6·96	19·26	19·34
CH_3	$CH_2N(CH_3)(C_6H_5)$	30	B	104°	61	$C_{17}H_{17}ON_3$	72·93	73·09	6·02	6·13	14·91	15·04
CH_3		40	B	106°	70	$C_{15}H_{19}ON_3$	69·92	70·00	7·35	7·44	16·17	16·33
CH_3		30	D	114°	73	$C_{14}H_{17}O_2N_3$	64·80	64·84	6·56	6·61	16·01	16·21

TABLE 2 (Contd)

		Volume of methanol, ml.	Solvent of crystallization[a]	M.p.[b]	Yield, %	Formula	Carbon, %		Hydrogen, %		Nitrogen, %	
							Found	Calc.	Found	Calc.	Found	Calc.
C_6H_5	$CH_2N(CH_3)_2$	30	D	132°	79	$C_{17}H_{17}ON_3$	72·81	73·09	6·00	6·13	14·92	15·04
C_6H_5	$CH_2N(CH_3)(C_6H_5)$	60	B	140°	68	$C_{22}H_{19}ON_3$	77·18	77·39	5·42	5·61	12·10	12·31
C_6H_5	$CH_2N(C_2H_5)(C_6H_5)$	75	B	112°	66	$C_{23}H_{21}ON_3$	77·61	77·72	6·20	5·96	13·67	11·82
C_6H_5		85	B	168°	75	$C_{20}H_{21}ON_3$	75·59	75·21	7·31	6·63	13·54	13·16
C_6H_5		85	B	177°	80	$C_{19}H_{19}O_2N_3$	70·84	71·01	5·91	5·96	12·77	13·08
						Bis-Derivatives (II)						
	Compound (II)											
R =												
H		20	E	139°	63	$C_{20}H_{19}O_2N_5$	66·40	66·47	5·18	5·30	19·18	19·38
CH_3		20	E	102°	61	$C_{22}H_{23}O_2N_5$	66·67	67·85	5·82	5·95	17·84	17·98
C_6H_5		30	B	166°	65	$C_{32}H_{27}O_2N_6$	74·74	74·83	5·43	5·30	14·16	13·64

			2-Aminomethyl Derivatives of 4,5-Dihydro-6-phenyl-3(2H)-pyridazinones								
Compound											
IIIc	10	D	118°	71	$C_{16}H_{21}ON_3$	70·61	70·82	8·04	7·80	15·32	15·49
IIId	10	D	105°	66	$C_{15}H_{19}O_2N_3$	65·74	65·91	6·88	7·01	15·18	15·37
IVi	20	B	117°	72	$C_{23}H_{25}ON_3$	76·56	76·85	7·22	7·01	11·48	11·69
IVj	50	D	120°	74	$C_{23}H_{24}O_3N_4$	68·17	68·30	5·78	5·98	13·80	13·85
			4-Aminomethyl Derivatives of 3-Methyl-2-phenyl-3-pyrazolin-5-ones								
Compound											
Vd	50	A	178°	81	$C_{16}H_{21}ON_3$	70·55	70·82	7·64	7·80	15·32	15·49
Ve	50	B	198°	84	$C_{15}H_{19}O_2N_3$	65·73	65·91	6·97	7·01	15·12	15·37
			Bis-Derivatives								
Compound (VI) R =											
C_2H_5	50	F	172°	71	$C_{24}H_{27}O_2N_5$	68·73	69·04	6·49	6·52	16·53	16·78
C_6H_5	50	B	182°	78	$C_{28}H_{27}O_2N_5$	72·11	72·23	5·62	5·85	15·13	15·04
$C_6H_4CH_3$—o	50	B	155°	74	$C_{29}H_{29}O_2N_5$	72·41	72·63	5·96	6·10	14·45	14·61
$C_6H_4CH_3$—p	50	B	164°	76	$C_{29}H_{29}O_2N_5$	72·34	72·63	5·84	6·10	14·34	14·61

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[a] A, methyl alcohol; B, ethyl alcohol; C, benzene; D, petroleum ether (b.p. 60–80°); E, benzene–pet. ether mixture; F, acetone–alcohol mixture,

[b] All m.ps. are uncorrected.

Action of piperidine

(a) *On 2-hydroxymethyl derivatives* (Ie *and* IIIe). To a hot solution of the hydroxymethyl derivative (Ie, R = H, CH_3, C_6H_5, or IIIe; 1·0 g) in methanol (50 ml), piperidine (1·0 ml) was added; the mixture was refluxed 10 min and left to cool. The crystals which separated proved to be the corresponding 2-N-piperidinomethyl derivatives, yields 84, 83, 87, 81 %, respectively.

When a mixture of 2-hydroxymethyl-4-phenyl-1(2H)-phthalazinone (Ie, R = C_6H_5; 1·0 g) and piperidine (1·0 ml), in the absence of methanol, was heated on a boiling water-bath for 15 min, followed by cooling, 4-phenyl-1(2H)-phthalazinone (Ic; 0·7 g) was obtained.

(b) *On 2-chloromethyl-*1(2H)*-phthalazinones* (If). To a suspension of 2-chloromethyl-4-methyl-1(2H)-phthalazinone (If, R = CH_3; 1·0 g) in ether (50 ml), piperidine (2·0 ml) was added. The mixture was refluxed for 30 min and filtered while hot from the insoluble piperidine hydrochloride. The solid (1·0 g), obtained upon evaporation of the ether, was crystallized from alcohol and proved to be 4-methyl-2-N-piperidinomethyl-1(2H)-phthalazinone (Id, R = CH_3; R′ = N-piperidinomethyl).

Similarly, treatment of 2-chloromethyl-4-phenyl-1(2H)-phthalazinone (If, R = C_6H_5) with piperidine as described, yielded 4-phenyl-2-N-piperidinomethyl-1(2H)-phthalazinone (Id, R = C_6H_5; R′ = N-piperidinomethyl) in 91 % yield.

4-*Arylthiomethyl-*3*-methyl-*2*-phenyl-*3*-pyrazolin-*5*-ones* (Vf–i)

General procedure. A mixture of Vd (0·01 mole) and the appropriate aromatic thiol (0·02 mole) was heated (oil-bath) at 150° for 2 hr and allowed to cool. The oily residue was triturated with alcohol. The resulting solid was crystallized from alcohol.

4-Phenylthiomethyl-3-methyl-2-phenyl-3-pyrazolin-5-one (Vf) formed colourless prisms, m.p. 202°, yield, 77 %. (Found: C, 68·62; H, 5·63; N, 9·31; S, 10·85. $C_{17}H_{16}ON_2S$ requires: C, 68·92; H, 5·41; N, 9·46; A, 10·81 %). Vf was also obtained by treating the bis-derivative (VI, R = C_6H_5) with thiophenol as described above.

4-*o*-Tolylthiomethyl-3-methyl-2-phenyl-3-pyrazolin-5-one (Vg) formed colourless prisms, m.p. 198°, yield, 73 %. (Found: C, 69·53; H, 5·72; N, 8·98; S, 10·11. $C_{18}H_{18}ON_2S$ requires: C, 69·68; H, 5·81; N, 9·03; S, 10·32 %).

4-*m*-Tolylthiomethyl-3-methyl-2-phenyl-3-pyrazolin-5-one (Vh) formed colourless prisms, m.p. 168°, yield 70 %. (Found: S, 10·21. $C_{18}H_{18}ON_2S$ requires: S, 10·32 %).

4-*p*-Tolylthiomethyl-3-methyl-2-phenyl-3-pyrazolin-5-one (Vi) formed colourless needles, m.p. 170°, yield 74 %. (Found: S, 10·63. $C_{18}H_{18}ON_2S$ requires: S, 10·32 %).

Vf–i are all soluble in warm NaOH aq. and give a yellow colour with conc. H_2SO_4.

Action of diazomethane on Vf–i. An ethereal solution of diazomethane (prepared from 4 g nitrosomethylurea) was added to the appropriate arylthiomethyl derivative (Vf–i; 1·0 g) and the reaction mixture kept overnight in a refrigerator. The oily residue, obtained upon evaporation of the ether, was washed several times with pet. ether (b.p. 50–70°) and the resulting solid crystallized from alcohol.

The methylated products (VII), listed in Table 3, are colourless, insoluble in NaOHaq., give no colour with $FeCl_3$ solution and develop a pale yellow colour with conc. H_2SO_4.

Cyanoethylation of 1(2H)*-phthalazinones* (Ia–c) and 4,5*-dihydro-*6*-phenyl-*3(2H)*-pyridazinones* (IIIa, IVa–b)

The appropriate compound (0·01 mole) was added to a solution of pyridine (50 mole) and water (10 ml) containing acrylonitrile (3 ml) and was refluxed 3 hr. The reaction mixture was cooled and diluted with water and the solid product obtained recrystallized (cf. Table 4). In cases where no solid was obtained upon dilution with water, the product was isolated by extraction with benzene and evaporation of the benzene layer.

The cyanoethyl derivatives (Ig, IIIf, and IVk–l) listed in Table 4 are all colourless and soluble in dil. HCl. Compounds Ig and IIIf give no colour with conc. H_2SO_4 but IVk–l develop a yellow colour with the same reagent.

1(2H)*-Phthalazinone-*2*β-propionic acids* (Ih). A suspension of the cyanoethyl derivative (Ig: 0·005 mole) in 1 N NaOH (15 ml) was refluxed 1 hr and cooled. The solid, which separated upon acidification with HCl aq. was filtered off and crystallized from benzene.

1(2H)-Phthalazinone-2β-propionic acid (Ih, R = H) formed colourless needles, m.p. 144°, yield 76 %. (Found: C, 59·95; H, 4·53; N, 13·08. $C_{11}H_{10}O_3N_2$ requires: C, 60·55; H, 4·59; N, 12·84 %).

TABLE 3. PRODUCTS OF DIAZOMETHANE WITH 4-ARYLTHIOMETHYL-3-METHYL-2-PHENYL-3-PYRAZOLIN-5-ONES (Vf–i)

Product (VII) Ar =	M.p.[a]	Yield, %	Formula	Carbon, %		Hydrogen, %		Nitrogen, %		Sulphur, %	
				Found	Calc.	Found	Calc.	Found	Calc.	Found	Calc.
C_6H_5	80°	67	$C_{18}H_{18}ON_2S$	69·23	69·68	5·67	5·81	9·14	9·03	10·35	10·32
$C_6H_4CH_3$—o	94°	63	$C_{19}H_{20}ON_2S$	70·12	70·37	5·83	6·17	8·52	8·64	9·53	9·88
$C_6H_4CH_3$—m	62°	61	$C_{19}H_{20}ON_2S$							9·62	9·88
$C_6H_4CH_3$—p	102	65	$C_{19}H_{20}ON_2S$							9·70	9·88

[a] All m.p.s are uncorrected.

TABLE 4

	Solvent of crystallization[a]	M.p.[b]	Yield, %	Formula	Carbon, %		Hydrogen, %		Nitrogen, %	
					Found	Calc.	Found	Calc.	Found	Calc.
Compound Ig, R =				2-Cyanoethyl-1(2H)-phthalazinones						
H	A	112°	64	$C_{11}H_9ON_3$	66·11	66·33	4·42	4·55	19·89	21·10
CH_3	A	120°	68	$C_{12}H_{11}ON_3$	68·19	67·59	5·34	5·20	19·98	19·71
C_6H_5	B	142°	73	$C_{17}H_{13}ON_3$	74·13	74·16	4·94	4·76	15·65	15·26
				2-Cyanoethyl-4,5-dihydro-6-phenyl-3-2(H)-pyridazinones						
Compound										
IIIf	C	65°	62	$C_{13}H_{13}ON_3$	68·70	68·70	5·95	5·77	18·32	18·49
IVk	C	96°	71	$C_{20}H_{17}ON_3$	66·84	76·17	5·31	5·43	13·11	13·33
IVl	B	164°	73	$C_{20}H_{16}O_3N_4$	66·63	66·66	4·25	4.48	15·32	15·55

[a] A, pet ether (b.p. 60–80°); B, alcohol; C, alcohol–water mixture

[b] M.p.s are uncorrected.

4-Methyl-1(2H)-phthalazinone-2-β-propionic acid (Ih, R = CH_3) formed colourless needles, m.p. 131°, yield 81%. (Found: C, 61·95; H, 5·01; N, 11·91. $C_{12}H_{12}O_3N_2$ requires: C, 62·07; H, 5·17; N, 12·07%).

4-Phenyl-1(2H)-phthalazinone-2-β-propionic acid (Ih, R = C_6H_5) formed colourless needles, m.p. 188°, yield 85%. (Found: C, 69·18; H, 4·78; N, 9·66. $C_{17}H_{14}O_3N_2$ requires: C, 69·39; H, 4·76; N, 9·52%).

Action of phenylmagnesium bromide

(a) *On* 2-N-*piperidinomethyl*-4-*phenyl*-1(2H)-*phthalazinone*. To an ethereal solution of PhMgBr (prepared from 0·9 g Mg, 8·0 g, bromobenzene and 40 ml dry ether) was added a solution of Id (R = N-piperidinomethyl) (1·5 g) in dry benzene (50 ml). The reaction mixture was refluxed (steam-bath) 2 hr, set aside at room temp. overnight, and then decomposed with a cold, saturated NH_4Cl aq. The reaction mixture was extracted with ether; the ethereal layer dried (Na_2SO_4) and then allowed to evaporate slowly. The oily residue was washed several times with hot pet. ether (b.p. 40–60°) and crystallized from benzene as colourless crystals (0·95 g), m.p. 194°, not depressed when mixed with an authentic sample of 1,4-diphenylphthalazine.[18]

(b) *On* 2-N-*piperidinomethyl*-4,5-*dihydro*-6-*phenyl*-3(2H)-*pyridazinone* (IIIc). A solution of IIIc (1·5 g) in dry benzene (50 ml) was treated with PhMgBr and the reaction mixture worked up as described. The oily residue was washed several times with hot pet. ether and crystallized from benzene as colourless crystals (0·87 g), m.p. 221°, not depressed when mixed with an authentic sample of 3,6-diphenylpyridazine.[23]

(c) *On* 4,5-*dihydro*-6-*phenyl*-3(2H)-*pyridazinone* (IIIa). Treatment of IIIa (1·5 g) with PhMgBr as described, gave 3,6-diphenylpyridazine (1·3 g) identified by m.p. and mixed m.p.

(d) *On* 6-*phenyl*-3(2H)-*pyridazinone*. 3,6-Diphenylpyridazine (1·0 g) was also obtained by treatment of 6-phenyl-3(2H)-pyridazinone (1·5 g) with PhMgBr in the usual manner.

The IR spectra were measured in nujol solution using a Perkin–Elmer model 137B.

[23] C. Paal and H. Schulze, *Ber.* **33**, 3798 (1900).