PART-II
The fully unsaturated five membered compounds having two heteroatoms (Nitrogen, Sulphur and Oxygen) and two double bonds comprised two important series with the heteroatoms in positions 1,2 and 1,3. The more comprehensively studied is that with heteroatoms in the 1,2 positions and includes pyrazole (1) which was first synthesised in 1883 by Knorr and Isoxazole (2) obtained five decades later. The Isothiazole (3), has been studied very little, and relatively few compounds containing this ring are known.

Antipyrine (4), discovered in 1884 by Knorr, spurred a search for other 5-pyrazolone derivatives, resulting in the discovery of aminopyrine (5), followed by phenylbutazone (6) and oxyphenbutazone (7). Some of these drugs are used in therapy for their antiinflammatory and analgesic properties even today.
Recently, pyrazole derivatives have been found wide applications in industry as bleaching agents, luminescent and fluorescent substances, systemic insecticides and plant growth stimulants. Pyrazole derivatives have also exhibited a wide variety of pharmacological activities, such as analgesic, antiinflammatory, sedative, antiulcer, cholinesterase inhibitory, bacteriostatic, bactericidal and fungicidal activities.

Because of their wide applications in industry and medicine, pyrazole derivatives continue to attract the attention of organic chemists.

**Pyrazole synthesis:**

In the recent years, the synthesis of pyrazole derivatives by ring closure reaction of appropriate open-chain intermediates has attracted considerable attention.

The various synthetic routes to pyrazoles by ring closure reaction have been classified according to the bond formed in the cyclization step. Among the variety of routes available for the synthesis of pyrazole derivatives, the method involving the intermolecular Michael addition type cyclization of hydrazine with an appropriate nitriles like α-chloroacrylonitriles, β-alkoxy acrylonitriles, α-β-dichloro propionitriles, malononitriles, β-ketonitriles allenic or acetylenic nitriles and β-chlorocinnammonitriles have extensively been studied.

**Synthesis of 3-Amino Pyrazoles:**

Following are the different routes for the synthesis of 3-amino pyrazoles.
(a) From α-chloroacrylonitriles and β-alkoxy acrylonitriles:

3-Amino pyrazole (9) has been prepared by the base catalysed condensation of α-chloroacrylonitrile (8)\textsuperscript{15-17} and β-alkoxyacrylonitrile (10)\textsuperscript{18,19} with hydrazine hydrate in aqueous medium.

\[ \text{Cl} \text{C} = \text{C} \text{N} \xrightarrow{\text{N}_2\text{H}_4\cdot\text{H}_2\text{O}} \text{N} = \text{C} \text{NH}_2 \xrightarrow{\text{N}_2\text{H}_4\cdot\text{H}_2\text{O}} \text{H} \text{C} = \text{C} \text{N} \]

(8) \hspace{1cm} (9) \hspace{1cm} (10)

\[ R = \text{alkyl} \]

Recently, the synthesis of 4,5-substituted-3-aminopyrazoles (12) by the reaction of [bis(methylthio)methylene]cyanoacetonilides (11) with hydrazine has been described.\textsuperscript{21}

\[ \text{R-NHCO} \text{C} = \text{C} \text{N} \xrightarrow{\text{N}_2\text{H}_4\cdot\text{H}_2\text{O}} \text{CONH-R} \]

(11) \hspace{1cm} (12)

where: \( R^1 = -\text{S-CH}_3, -\text{NR}_2\text{R}^3 \)

\( R = \text{C}_6\text{H}_5-, 4-\text{CH}_3-\text{C}_6\text{H}_4-, 4-\text{H}_2\text{CO-} \text{C}_6\text{H}_4- \)

α-Nitro-β,β-bis(benzylamino)acrylonitrile (13) was cyclocondensed with hydrazine to give 3-amino-5(benzylamino)-4-nitropyrazole (14).\textsuperscript{22}

\[ \text{O}_2\text{N} \text{C} = \text{C} \text{N} \xrightarrow{\text{N}_2\text{H}_4\cdot\text{H}_2\text{O}} \text{Ph-CH}_2\text{HN} \text{N} \text{NH-CH}_2\text{-Ph} \]

(13) \hspace{1cm} (14)
(b) From malononitriles:

Cyclocondensation of alkoxyethylene malononitrile (15) with hydrazine gave 3-amino-4-cyanopyrazole (16) in 85% yield.

\[
\text{NC} \quad \text{CN} \quad \xrightarrow{\text{N}_2\text{H}_4\cdot\text{H}_2\text{O}} \quad \text{CN} \quad \text{NH}_2
\]

(15) \quad (16)

where: \( R = \text{H}, \text{CH}_3, \text{C}_6\text{H}_5, \text{4-CH}_3\text{-C}_6\text{H}_4 \)

\( R^1 = -\text{CH}_3, -\text{C}_2\text{H}_5 \)

3-Cyanomethyl-4-cyano-5-aminopyrazole (18) was found by the reaction of malononitrile with hydrazine. The reaction involved dimerization of malononitrile under the influence of the strongly basic hydrazine, followed by reaction of the latter with the dimer, with evolution of ammonia. The same compound was also obtained independently by the reaction of hydrazine with the dimer of malononitrile (1,1,3-tricyano-2-aminopropene-1) (17).

\[
\text{NC} \quad \text{CN} \quad \text{NC-CH}_2 \quad \text{NH}_2 \quad \xrightarrow{\text{N}_2\text{H}_4\cdot\text{H}_2\text{O}} \quad \text{NC-CH}_2 \quad \text{NH}_2
\]

(17) \quad (18)

(c) From β-Ketonitriles:

The reaction of 4-substituted benzyloacetonitriles (19) with hydrazine in ethanol gave 5-amino-3-substituted pyrazoles (20).

\[
\text{NC} \quad \xrightarrow{\text{N}_2\text{H}_4\cdot\text{H}_2\text{O}} \quad \text{NH}_2
\]

(19) \quad (20) \quad X=\text{H},\text{F}
(d) From allenic or acetylenic nitriles:

The double Michael addition of 2,3-butadienenitrile (21) with hydrazine hydrate gave 3-amino-5-substituted pyrazole (22).\(^{30,31}\) 3-Amino-5-substituted pyrazole (24) has also been synthesised by the reaction of acetylenic nitriles (23)\(^{32}\) with hydrazine hydrate.

\[
\begin{align*}
\text{(21)} & \quad \text{CN} \\
\text{(22)} & \quad \text{H} \\
\text{(23)} & \quad \text{NH}_2 \\
\text{(24)} & \quad \text{NH}_2
\end{align*}
\]

where: \(R, R' = \text{-CH}_3, \text{-C}_2\text{H}_5\)

(e) From \(\beta\)-chlorocinnamonitriles:

H. Hartmann and J. Liebscher synthesised 3-amino-5-substituted pyrazoles (26) by the reaction of \(\beta\)-chlorocinnamonitriles (25)\(^{33-39}\) with hydrazine hydrate in aqueous medium in good yield.

\[
\begin{align*}
\text{(25)} & \quad \text{CN} \\
\text{(26)} & \quad \text{NH}_2
\end{align*}
\]

where: \(R = \text{-H, -CH}_3, \text{-OCH}_3, \text{-Cl, -Br, -NO}_2, \text{-C}_6\text{H}_5}\)
(f) From acyliminoester or propionitriles:

3-Amino-5-substituted pyrazole (28) have been synthesised from acyliminoester hydrochloride (27) and hydrazine hydrate in 92% yield.\textsuperscript{40}

\[
\begin{align*}
\text{HN} & \text{C} & \text{OEt} \\
\text{HCl} & \text{C} & \text{H}_2 \\
\text{C} & \text{N} & \text{NH}_2 \\
(27) & & (28) R=\text{CMe}_3
\end{align*}
\]

M.H. Elnagdi et al.\textsuperscript{41} have synthesised 5-amino-4-p-chlorophenylazo-3-phenyl pyrazole (30) from 2-p-chlorophenylhydrazone-3-keto-3-phenylpropionitrile (29) and hydrazine hydrate.

\[
\begin{align*}
\text{P} & \text{-Cl} & \text{C}_6 & \text{H}_4 & \text{N}=\text{N} & \text{CN} \\
\text{H}_5 & \text{C}_6 & \text{N} & \text{CN} \\
(29) & & (30)
\end{align*}
\]

(g) From β-aminocrotonitrile or α-formyl phenyl acetonitrile:

β-Aminocrotonitrile (31) and α-formyl phenyl acetonitrile (33) with hydrazine hydrate gave their corresponding 3-amino-5-methyl pyrazole (32) and 3-amino-4-phenyl pyrazole (34) respectively.\textsuperscript{42}

\[
\begin{align*}
\text{H} & \text{C} & \text{CN} \\
\text{H}_3 & \text{C} & \text{NH}_2 \\
(31) & & (32)
\end{align*}
\]

\[
\begin{align*}
\text{H} & \text{C} & \text{CN} \\
\text{H}_5 & \text{C}_6 & \text{CO} \\
(33) & & (34)
\end{align*}
\]
Pyrazolotriazines:

Pyrazolotriazines are bicyclic bridgehead nitrogen heterocycles having in common a pyrazole nucleus fused to a triazine ring. They give rise to two positional isomers.

Pyrazolo[1,5-a]-1,3,5-triazine (I)
Pyrazolo[1,5-c]-1,2,5-triazine (II)

The methods of synthesis and the chemistry of condensed bridgehead nitrogen containing heterocycles, pyrazolotriazines have been reviewed by D.E. O'Brien and co-workers. 43

Synthetic routes to pyrazolo[1,5-a]-1,3,5-triazines:

A variety of interesting biological activities of pyrazolo[1,5-a]-1,3,5-triazines have given impetus to the synthesis of its derivatives. However, only a limited numbers of synthetic routes with wide applicability have been developed.

Herein an attempt has been made to review some recent reports on the synthesis of pyrazolo[1,5-a]-1,3,5-triazines. The methods of synthesis of condensed pyrazolo[1,5-a]-1,3,5-triazines are classified according to the number of components employed in the synthesis.
Construction of triazine on pyrazole:

This approach has been widely used for the synthesis of pyrazolo-[1,5-a]-1,3,5-triazines. Many of the synthesis utilise 3-aminopyrazole derivatives.

The 3-amino pyrazoles have been reacted with reagents such as isothiocyanates, imidate ester, orthoester, $\beta$-ketonitrile, cyanoguanidine, diethoxy methylene acetate and 1,3-dialkyl-5-azauracil in a single step to obtain the triazine ring directly or alternatively these have been converted to intermediates which were cyclized to the desired pyrazolo[1,5-a]-1,3,5-triazines.

(I) One step cyclization of pyrazoles:

(a) Condensation with $N,N$ bis(chlorocarbonyl)isopropylamine:

Condensation of $N,N$ bis(chlorocarbonyl)isopropylamine (36) with 3-aminopyrazoles (35) afforded 3,7,8-substituted pyrazolo[1,5-a]-1,3,5-triazine-2,4-(1H)-dions (37) in one step.

where: $R^1 = H$, alkyl, halogen, cyano, $NO_2$, $CONH_2$, cycloamine
$R^2 = H$, alkyl, amino, alkoxy, alkylthio
(b) Condensation with monothiodiacylamines or N-aryltrithiimidates:

T.W. Strohmeyer and co-workers\textsuperscript{46} have reported the use of some monothiodiacylamines (39) in the condensation with 3-aminopyrazoles (38) to obtain 2,4-dialkyl/aryl pyrazolo[1,5-a]-1,3,5-triazines (40).

\[ \text{(38)} \rightarrow \text{(39)} \rightarrow \text{(40)} \]

where: \( R^2 = \text{H, Ph}, \text{2-C}_4\text{H}_5\text{O}^- \), \( 2-\text{C}_4\text{H}_3\text{S}^- \)

\( R = \text{4-CF}_3-\text{C}_6\text{H}_4^-, \text{4-Cl-C}_6\text{H}_4^- \)

\( R^1 = \text{C}_6\text{H}_5^-, \text{CH}_3^-, \text{4-Cl-C}_6\text{H}_4^- \)

(c) Condensation with cyanoguanidine:

In one of the earlier syntheses of 2,4-diamino-7-phenyl pyrazolo[1,5-a]-1,3,5-triazine (42), the condensation of cyanoguanidine (41)\textsuperscript{47,48} with 3-amino-5-phenyl pyrazole (38) has been used as a method of synthesis.\textsuperscript{49-51}

\[ \text{(38)} \rightarrow \text{(41)} \rightarrow \text{(42)} \]

where: \( R = \text{CH}_3^-, \text{Ph}^- \)
(d) **Condensation with 1,3-dialkyl-5-azauracil:**

1,3-Dimethyl-5-azauracil (44), a versatile synthon for the synthesis of various heterocycles, reacted readily with 3-aminopyrazoles (43) in sodium ethoxide to give the corresponding pyrazolo[1,5-a]-1,3,5-triazines (45).\(^{52}\)

\[
\begin{align*}
\text{NH}_2 \quad \text{NH} & \quad \text{CH}_3 \quad \text{CH}_3
\end{align*}
\]

(43)

\[
\begin{align*}
\text{N} \quad \text{N} \quad \text{O} & \quad \text{CH}_3 \quad \text{CH}_3 \quad \text{N} \quad \text{N} \quad \text{N} \quad \text{O} \quad \text{NH} \quad \text{CH}_3 \quad \text{C} \quad \text{O}
\end{align*}
\]

(44)

(45)

where: \( R = -\text{CH}_3, -\text{C}_2\text{H}_5, -\text{COOEt, -C-nucleosides} \)

(e) **Condensation with N-cyanoformimidate:**

A direct condensation of 3-aminopyrazoles (46) with ethyl-N-cyanoformimidate (47) gave 4-aminopyrazolo[1,5-a]-1,3,5-triazines (48).\(^{53,54}\)

\[
\begin{align*}
\text{NH}_2 \quad \text{NH} & \quad \text{EtO} \quad \text{C} \quad \text{H} \quad \text{N} \quad \text{C} \quad \text{N} \quad \text{NH}_2
\end{align*}
\]

(46)

(47)

(48)

where: \( R = \text{H} \)

= 5'-O-trityl-β-D-ribofuranosyl
(f) **Condensation with orthoester:**

7,8-Substituted pyrazolo[1,5-a]-1,3,5-triazine-4(1H)-ones (49a) were prepared by cyclizing the (un)substituted pyrazoles (49) with triethylorthoformate.\(^{55-59}\)

\[
\begin{array}{c}
\text{R} \\
\text{R}_1 \\
\text{N} \\
\text{C} \\
\text{NH}_2 \\
\text{X} \\
\text{R}_2 \\
\text{H} \\
\text{OEt} \\
\text{EtOEt} \\
\text{R}_3 \\
\end{array}
\]

(49)

\[
\begin{array}{c}
\text{R} \\
\text{R}_1 \\
\text{N} \\
\text{C} \\
\text{NH}_2 \\
\text{X} \\
\text{R}_2 \\
\text{H} \\
\text{OEt} \\
\text{EtOEt} \\
\text{R}_3 \\
\end{array}
\]

(49a)

where: \( R_1 = H, C_6H_5, 4-CH_3-C_6H_4, SCH_3 \)

\( R_2 = R_3 = H \)

\( X = NH, O, S. \)

\( R = H, \beta-D-\text{ribofuranosyl, COOEt} \)

(g) **Condensation with isothiocyanate or aminonitrile:**

Iminopyrazolines (50) on reaction with substituted isothiocyanates (51) gave 2,4-dithioxa-3-substituted pyrazolo[1,5-a]-1;3,5-triazinen (52)\(^{50,55}\) in one step.

\[
\begin{array}{c}
\text{R} \\
\text{N} \\
\text{C} \\
\text{S} \\
\text{R}_2 \\
\end{array}
\]

(50)

\[
\begin{array}{c}
\text{R} \\
\text{N} \\
\text{C} \\
\text{S} \\
\text{R}_1 \\
\end{array}
\]

(52)

where: \( R = H, C1 \)

\( R_1 = \text{Et, Ph, 4-Cl-C}_6\text{H}_4 \)
In the same manner iminopyrazolines (50) on direct condensation with aminonitrile gave the corresponding substituted pyrazolo[1,5-\(a\)]-1,3,5-triazines (53).
(II) Cyclization involving open chain intermediate of pyrazoles:
(a) Formation of amidines and cyclization:

3-Aminopyrazoles (54) undergo normal reaction with ethyl N-carbethoxyformimidate (55) in ethanol to give N-carbethoxy-N'-{(3-pyrazolyl)formamidine (56) which on cyclization in potassium carbonate in ethanol or in xylene gave 4-oxo-3H-pyrazolo[1,5-a]-1,3,5-triazine (57).\(^{53}\)
3-Amino-5-phenylpyrazole,\textsuperscript{39} or 3-amino-5-substituted phenyl pyrazole (58)\textsuperscript{39} was treated with the corresponding alkylethylimidate (59) in acetonitrile to give the corresponding N-(pyrazol-3-yl alkyl)amidines (60). Ring closure of (60) with the requisite alkyl triethyl orthoester (61) gave the corresponding 2,4-dialkyl-7-phenyl or substituted phenyl pyrazolo[1,5-a]-1,3,5-triazines (62).\textsuperscript{58,59,61,62}

Ring closure could also be accomplished by the appropriate anhydride\textsuperscript{61} to give the product (63). Ring closure with cyanogenbromide yielded their corresponding 2-alkyl-4-amino-7-phenylpyrazolo[1,5-a]-1,3,5-triazines (64).\textsuperscript{58}
where: (62) \( R_1 = H, \text{CH}_3, \text{SCH}_3, \text{C}_2\text{H}_5 \)
\( R_2 = H, \text{CH}_3, \text{C}_2\text{H}_5, \text{n-C}_3\text{H}_7, \text{C}_6\text{H}_5, \text{SCH}_3 \)
\( \text{OCH}_3, \text{OC}_2\text{H}_5, \text{N(C}_2\text{H}_5)_2, \text{NH-n-C}_4\text{H}_9 \)
\( R_3 = H, \text{C}_6\text{H}_5, 4-\text{CH}_3\text{O-C}_6\text{H}_4, 2-\text{CH}_3\text{O-C}_6\text{H}_4 \)
\( R_4 = H, \text{C}_6\text{H}_5, \text{Cl}, \text{COOC}_2\text{H}_5, \text{CN} \)

(63) \( R_1 = H, \text{CH}_3, \text{SCH}_3, \text{C}_2\text{H}_5 \)
\( R_2 = \text{CH}_3, \text{C}_2\text{H}_5, \text{n-C}_3\text{H}_7, \text{C}_6\text{H}_5 \)
\( R_3 = H, \text{C}_6\text{H}_5, 4-\text{CH}_3\text{O-C}_6\text{H}_4, 2-\text{CH}_3\text{O-C}_6\text{H}_4 \)
\( R_4 = H, \text{Br}, \text{Cl}, \text{CN}, \text{COOC}_2\text{H}_5, \text{C}_6\text{H}_5 \)

(64) \( R_1 = H, \text{CH}_3, \text{SCH}_3, \text{C}_2\text{H}_5 \)
\( R_3 = H, \text{C}_6\text{H}_5, 4-\text{CH}_3\text{O-C}_6\text{H}_4, 2-\text{CH}_3\text{O-C}_6\text{H}_4 \)
\( R_4 = H, \text{Br}, \text{Cl}, \text{CN}, \text{COOC}_2\text{H}_5, \text{C}_6\text{H}_5 \)

(b) Formation of thiourea and cyclization:

Various 3-amino-(un)substituted pyrazoles (65) have been reacted with ethoxy carbonyl isothiocyanate (66) to give thioureas (67). Cyclization of thiourea in basic medium like sodium hydroxide,\textsuperscript{63,64} pyridine\textsuperscript{65} and in triethylamine\textsuperscript{65} gave their corresponding pyrazolo[1,5-a]-1,3,5-triazines (68)\textsuperscript{19,63-65}.

\[ R_1 \text{N}=\text{NH}_{2} \]
\[ \text{EtO-C-NCS} \]
\[ \text{(65)} \]
\[ \rightarrow \]
\[ \text{R}_1 \text{N}=\text{N} \text{S} \]
\[ \text{EtO-C-O} \]
\[ \text{(66)} \]
\[ \rightarrow \]
\[ \text{R}_1 \text{N}=\text{N} \text{S} \]
\[ \text{EtO-C-O} \]
\[ \text{(67)} \]
\[ \rightarrow \]
\[ \text{R}_1 \text{N}=\text{N} \text{O} \]
\[ \text{(68)} \]
J. Kobe and co-workers\textsuperscript{59,66} have synthesised 7-phenylpyrazolo-[1,5-a]-1,3,5-triazine-4(3H)-thione (70) by the cyclocondensation of 3-amino-5-phenyl-2-thiocarbomoylpyrazole (69)\textsuperscript{56,67} with diethoxymethylacetate (DEMA).
Reactions of pyrazolo[1,5-a]-1,3,5-triazines:

Position 2 and 4 on the triazine ring in pyrazolo[1,5-a]-1,3,5-triazine are well suited for nucleophilic substitution, due to the neighbouring nitrogen atoms.

Electrophilic substitution reactions of pyrazolo[1,5-a]-1,3,5-triazine occur at position 8, as the electron density of the pyrazole moiety is further enhanced by the adjacent triazine ring.

\[
\text{\begin{array}{c}
\text{N} \\
\text{N}
\end{array}} \xrightarrow{E^+} \text{E} \text{\begin{array}{c}
\text{N} \\
\text{N}
\end{array}}
\]

Extensive work has been directed towards nucleophilic displacement reaction in the triazine ring\(^{19,44,52,53,56,58,59,61-64,66,68,69}\) and electrophilic substitution at position eight in pyrazole ring.\(^{59,61,62,64,66}\)

The stepwise synthesis via ring closure procedures of requisite pyrazole intermediates, followed by electrophilic substitution in the pyrazole ring and/or nucleophilic substitution in the 1,3,5-triazine moiety, resulted in the various pyrazolo[1,5-a]-1,3,5-triazines (Scheme-I, II, III).

There seems to be no report of direct nucleophilic substitution on pyrazolo[1,5-a]-1,3,5-triazine system.

The treatment of 2-methylthiopyrazolo[1,5-a]-1,3,5-triazine-4-one (71)\(^{59}\) with methyl iodide afforded 3-methyl-2-methylthiopyrazolo[1,5-a]-1,3,5-triazine-4-one (72). The structure of (72) was established by
removal of the methylthio group with Raney nickel to 3-methyl pyrazolo-[1,5-a]-1,3,5-triazine-4-one (74). Action of hydrogen peroxide on (72) yielded 3-methyl pyrazolo[1,5-a]-1,3,5-triazine-2,4-dione (73) in good yield. 3-Methyl pyrazolo[1,5-a]-1,3,5-triazine-2,4-dione (73) served as a useful starting material for the synthesis of the desired xanthines e.g. reaction of (73) with methyl iodide gave an analog of theophylline, 1,3-dimethylpyrazolo[1,5-a]-1,3,5-triazine-2,4-dione (75). The reaction of 1,3-dimethylpyrazolo[1,5-a]-1,3,5-triazine-2,4-dione (75) with N-bromosuccinimide in chloroform gave 8-bromo-1,3-dimethyl pyrazolo-(1,5-a)-1,3,5-triazine-2,4-dione (79).

Methylation of (73) with methyl iodide in dimethylformamide was carried out at the reflux temperature resulted in ring opening to give N-methyl-N'-pyrazol-3-yl methylurea (78). (Scheme-I).

\[
\begin{align*}
(71) & \quad \text{CH}_3\text{I} \\
& \downarrow \text{Raney Ni} \\
(72) & \quad \text{H}_2\text{O}_2 \\
& \downarrow \text{RI excess} \\
(74) & \quad \text{NBS} \\
(75) & \quad R = \text{CH}_3 \\
(76) & \quad R = \text{C}_2\text{H}_5 \\
(77) & \quad R = \cdot \text{n-C}_3\text{H}_7 \\
(78) & \quad \text{CH}_3\text{I} \\
& \downarrow \text{DMF} \\
(73) & \quad \text{NBS} \\
\end{align*}
\]
As noted in Scheme-II, reaction of 2-(methylthio)-4-chloropyrazolo[1,5-a]-1,3,5-triazine (80)\textsuperscript{59,66} with various primary and secondary amines in alcohol at steam bath temperature gave the 2-(methylthio)-4-(alkylamino)pyrazolo[1,5-a]-1,3,5-triazines (81). Treatment of 2-(methylthio)-4-chloro-8-bromopyrazolo[1,5-a]-1,3,5-triazine (82) with requisite amine afforded the 2-(methylthio)-4-(alkylamino)-8-bromopyrazolo[1,5-a]-1,3,5-triazine (83).

\textit{2-(Methylthio)-4-chloro-8-bromopyrazolo[1,5-a]-1,3,5-triazine (82)}\textsuperscript{58,66} when reacted with sodium hydrosulfide in aqueous ethanol gave 8-bromo-4-thio-2-(methylthio)pyrazolo[1,5-a]-1,3,5-triazine (84), which with methyl iodide gave 2,4-bis(methylthio)-8-bromopyrazolo[1,5-a]-1,3,5-triazine (85,86). Compound (82) has been reacted with various alcohol in basic condition to afforded 2-methylthio-4-alkoxy-8-bromopyrazolo[1,5-a]-1,3,5-triazine (87).\textsuperscript{58,61,66} (Scheme-II).
\[
\begin{align*}
(80) \quad & \text{Cl} \\
(82) & \text{Br} \\
(84) & \text{Br} \\
(85) & R = \text{CH}_3 \\
(86) & R = \text{C}_2\text{H}_5 \\
\end{align*}
\]

\[
\begin{align*}
\text{NBS} & \rightarrow \\
\text{NaSH} & \rightarrow \\
\text{RI} & \rightarrow \\
\text{ROH} & \text{NaHCO}_3 \\
\end{align*}
\]

\[
\begin{align*}
(81) \\
(83) \\
(84) \\
(87) \\
\end{align*}
\]

\[
\begin{align*}
\text{R-N-R} \\
\text{R-N-R} \\
\text{S-R} \\
\text{OR} \\
\end{align*}
\]

\[
\begin{align*}
\text{R} & = \text{CH}_3 \\
& = \text{CH}(\text{CH}_3)_2 \\
& = -\text{n-C}_3\text{H}_7
\end{align*}
\]
The reaction\textsuperscript{70} of the 4-hydrazino compound (90) with nitrous acid was of special interest because of the possible "tetrazolo-azido" equilibrium which might exist between (91a) (4-azido-7-phenyl pyrazolo[1,5-a]-1,3,5-triazine) and (91b) (10-phenyl tetrazolo[1,5-e]pyrazolo[1,5-a]-1,3,5-triazine). When 10-phenyl tetrazolo[1,5-e]pyrazolo[1,5-a]-1,3,5-triazine (91b) was refluxed in xylene for 98 hours, 4-amino-7-phenyl pyrazolo[1,5-a]-1,3,5-triazine (93) was obtained as the product. Alkaline hydrolysis of $91\text{a} \rightleftharpoons 91\text{b}$ gave a mixture of the amine (93) and the analogous "hydroxy" compound, 7-phenyl pyrazolo-[1,5-a]-1,3,5-triazin-4(3H)-one (92).

4-Hydrazino-7-phenyl pyrazolo[1,5-a]-1,3,5-triazine (90) was condensed with DEMA at room temperature to afford 8-phenyl triazolo[4,3-e]pyrazolo-[1,5-a]-1,3,5-triazine (94).\textsuperscript{70} Because of the low electron density at the nitrogen bridgehead, it was expected that isomerization of the tricyclic ring system would take place under acidic, basic or thermal condition.\textsuperscript{71-75}

Thus, compound (94) under thermal condition was heated to its melting point and maintained at that temperature for 5-minutes, the rearrangement was take place, yielded the isomeric 10-phenyl-5-triazolo[2,3-e]pyrazolo-[1,5-a]-1,3,5-triazine (95) which with 88% formic acid and concentrated hydrochloric acid gave 3-N-formamido-5-phenyl-2-5-triazolylypyrazole (96) and 3-amino-5-phenyl-2(2-5-triazolyly)pyrazole (97).\textsuperscript{64,66} (Scheme-III).
Application and important compounds:

Pyrazolo[1,5-a]-1,3,5-triazines exhibit a variety of biological activities. Biological properties of pyrazolo[1,5-a]-1,3,5-triazine are summarized below.

Cartwright and co-workers have prepared a series of 1,3,7,8-substituted pyrazolo[1,5-a]-1,3,5-triazine-2,4-diones (99) having Herbicidal activity at 10kg/ha preemergency gave 75% kill of e.g. wild-oats. $^{44,45}$

\[
\begin{align*}
\text{R} &= \text{Cycloalkyl, } C_{3-10} \text{ branched alkyl} \\
\text{R}^1 &= \text{H, alkyl, halogen, CN, NO}_2 \\
\text{R}^2 &= \text{H, alkyl, amino, alkoxy, alkylthio} \\
\text{R}^3 &= \text{H, alkyl}
\end{align*}
\]

8-β-D-Ribosylated derivatives of a pyrazolo[1,5-a]-1,3,5-triazine (100) are new type of C-nucleosides and potentially important precursor of analogues of the formycin. $^{19,52,53,56,69}$

\[
\begin{align*}
\text{where: } & R = \text{NH}_2, \text{OH} \\
\text{R}^1 &= 2',3'-\text{o-isopropylidine} \\
&= 5'-\text{o-trityl-β-D-ribofuranosyl}
\end{align*}
\]
A series of various pyrazolo[1,5-a]-1,3,5-triazines (101)\textsuperscript{52,61,63,64} have been prepared and studied as inhibitors of cAMP phosphodiesterase (PDE), isolated from bovine brain, bovine heart, and rabbit lung. A number of compounds were found to be superior to theophylline. 2-Ethyl-7-phenylpyrazolo[1,5-a]-1,3,5-triazine was found to be 97 times more potent than theophylline as an inhibitor of bovine brain PDE. 8-Bromo-2,4-dimethyl-7-phenylpyrazolo[1,5-a]-1,3,5-triazine showed $\propto_{\text{lung}} = 40$ compound to $\propto_{\text{heart}} = 3.0$. Thus, various substituents could increase or decrease the inhibition relative to the type and source of tissue from which the PDE was isolated. The most active compound was 8-bromo-4-(diethylamine)-7-phenyl pyrazolo[1,5-a]-1,3,5-triazine, which was 105 times more potent than theophylline as an inhibitor of PDE isolated from rabbit lung.

![Diagram](101)

where: $R = \text{OH, alkyl, alkoxy, halogen, SH, alkylthio, aralkylthio, alkylamine, hydrazino}$

$R^1 = H, \text{S-CH}_3$; $R^2 = H, \text{Halogen, CN, COOC}_2\text{H}_5$; $R^3 = H, \text{C}_6\text{H}_5$

A recent patent\textsuperscript{68} describes antiinflammatory activity in some 7-phenylpyrazolo-[1,5-a]-1,3,5-triazine (102,103) derivatives.

![Diagram](102)
where: \( R = \text{thioalkyl} \)

\( R^1 = \text{substituted amino} \)

\( = \text{N-heterocycloalkyl} \)

\[ \begin{array}{c}
\text{Ph} \\
\text{N} \text{~N} \text{~N} \text{~N} \text{~N} \\
\text{O} \\
\text{R} ^3 \text{~R} ^2 \text{~R} ^1 \\
\end{array} \]

(103)

where: \( R^2 = \text{thioalkyl, thioaralkyl, thioheteroaralkyl} \)

\( R^3 = \text{H, COO-alkyl, alkyl, allyl, PhCH}_2- \)

2-Methylthio-7-phenylpyrazolo[1,5-a]1,3,5-triazine derivative (104) was prepared, which inhibited ulcers caused by non-steroid analgesics and antiinflammatory agents. 76

\[ \begin{array}{c}
\text{Ph} \\
\text{N} \text{~N} \text{~N} \text{~N} \\
\text{S-CH}_3 \\
\text{R} \text{~N} \text{H} \text{~CH}_2\text{~S-CH}_2\text{~CH}_2\text{~NHMe}_2 \\
\end{array} \]

(104) \( R = \text{NH-CH}_2\text{~S-CH}_2\text{~CH}_2\text{~NHMe}_2 \)

A series of 4-aminopyrazolo[1,5-a]-1,3,5-triazines (105) have been prepared by A. Vogel and his co-workers62 as bronchodilator activity.

\[ \begin{array}{c}
\text{R} ^1 \text{~R} ^2 \text{~R} ^3 \\
\text{N} \text{~N} \text{~N} \\
\text{N} \text{~C} \text{~C} \\
\text{Ph} \\
\text{R} \text{~N} \text{H} \text{~CH}_2\text{~S-CH}_2\text{~CH}_2\text{~NHMe}_2 \\
\end{array} \]

(105)

where: \( R = \text{H, CH}_3, \text{Et, Cyclohexyl, OH} \)

\( R^1 = \text{NH}_2, \text{NMe}_2, \text{N(CH}_2\text{-CH=CH}_2)_2 \)

\( = \text{NH-NH}_2, \text{2-pyridylamino} \)

\( = \text{C}_{1-4}-\text{alkylamino} \)

\( R^2 = \text{H, CH}_3, \text{Cyclohexyl, Ph, Et} \)

\( R^3 = \text{H, Me, Cl, Br, NO}_2\text{ NH}_2, \text{NHAc, CH}_2\text{NMe}_2, \text{CHO} \)
Bronchodilator, antiallergic and antiinflammatory properties have been found in 2,4-diamino-7-methyl/phenylpyrazolo[1,5-a]-1,3,5-triazines (106)\textsuperscript{50,51} with a very low toxicity (2.5 to 5 times less than theophylline) provides a new potential agent for respiratory disease.

![Chemical structure](attachment:image.png)

\( R = \text{CH}_3, \text{C}_6\text{H}_5 \)
PRESENT WORK

The literature survey revealed that pyrazolo[1,5-a]-1,3,5-triazine derivatives are biologically active. However, their 3-N-aryl substituted derivatives have not been characterised or further worked out.

In the present study we pursued synthesis of various 3,7-diaryl pyrazolo[1,5-a]-1,3,5-triazine-2,4-(1H)-dione and their spectral analysis were studied. A series of 3-amino-5-aryl pyrazoles were synthesised from β-chlorocinnamonnitriles. 34 3-Amino-5-aryl pyrazoles on reaction with excess of ethylchloroformate gave ethyl-N-(5-aryl-2-carbethoxy pyrazol-3-yl)-carbamates.

Condensation of ethyl-N-(5-aryl-2-carbethoxy-pyrazol-3-yl)carbamates with various arylamine in ethanol using triethylamine as catalyst gave N2-aryl-N1-(5-aryl-2-carbethoxy pyrazol-3-yl)ureas.

[Diagram of molecule]

where:  \( R = H, CH_3, -OCH_3, -Cl, -Br, -C_6H_5 \)

\( R' = C_6H_5^-, 4-NO_2-C_6H_4^-, 4-HCO-C_6H_4^-, 4-Cl-C_6H_4^- \)
3,7-Diaryl pyrazolo[1,5-a]-1,3,5-triazine-2,4(1H)-diones were obtained in good yield by the intramolecular cyclization of symmetrical and asymmetrical disubstituted ureas in dry pyridine.

![Chemical Structure](V)

where: $R = -\text{H}, -\text{CH}_3, -\text{OCH}_3, -\text{Cl}, -\text{Br}, -\text{C}_6\text{H}_5$

$R^1 = 4-\text{Cl-}C_6\text{H}_4^-$
THEORETICAL

[A] Synthetic Study:

β-Chlorocinnamionitriles (I):

Chemical properties and preparation of β-chlorocinnamionitriles have been studied by H. Hartmann and co-workers. 35-39 It has been discussed in theoretical and experimental sections Part-I (p. 30 and p. 56) of the thesis.

3-Amino-5-aryl pyrazoles (II):

3-Amino-5-aryl pyrazoles (II) 33, 34 were prepared by short heating of β-chlorocinnamionitriles (I) with hydrazine hydrate in alcoholic solution.

\[
\begin{align*}
\text{R} & \text{-} \text{C} = \text{CH} - \text{CN} \\
\text{Cl} & \text{NH}_2 - \text{NH}_2 \cdot \text{H}_2 \text{O} \\
\text{NH}_2 - \text{NH}_2 \cdot \text{H}_2 \text{O} & \rightarrow \\
\text{R} & \text{-} \text{C} = \text{CH} - \text{CN} \quad (\text{Ia}) \\
\text{NH} & \text{-NH}_2 \\
\end{align*}
\]

where: \( R = -H, -\text{CH}_3, -\text{OCH}_3, -\text{Cl}, -\text{Br}, -\text{C}_6\text{H}_5 \)

β-Hydrazino cinnamionitriles (Ia) were assumed to be intermediate but have not been isolated. The 3-amino-5-aryl pyrazoles (II) formed can be isolated in high yield by meresuction of the reaction mixture with water. The structures of the 3-amino-5-aryl pyrazoles were confirmed by the spectral analysis.
Owing to the simple route, the employed β-chlorocinnaminitriles (I) by a modified Vilsmeier-Haak-Arnold reaction of acetophenones,\textsuperscript{36,37} the 3-aminopyrazole synthesis presented seems to be a reasonable alternative to the already published synthesis starting from α-chloroacrylonitriles,\textsuperscript{17} α,β-dichloro propionitriles,\textsuperscript{20} cyano acetonitriles\textsuperscript{77} or β-ketonitriles.\textsuperscript{29}

**Carbamates (III) and ureas (IV):**

Ureas and carbamates (urethanes) are the compounds of great biochemical interest and also are the starting materials for the preparation of a number of organic compounds of pharmacological importance. There are several common synthesis for derivatives of urea and urethane.

Following summarizes the synthetic methods,

(i) action of amine on phosgene,\textsuperscript{78-88}

(ii) action of amine or alcohol on isothiocyanates,\textsuperscript{89-93}

(iii) action of amine on urea or nitrourea,\textsuperscript{94-98}

(iv) action of ammonia or amines on chloroformates,\textsuperscript{99-103}

(v) action of alcohol on urea and urethane,\textsuperscript{104-107}

(vi) action of carbamyl chloride on alcohols or ammonia,\textsuperscript{108,109}

(vii) urea and alkylisoureas from cyanamides,\textsuperscript{110-111}

(viii) action of amine on urethane,\textsuperscript{112}
Among these methods, the action of amine on chloroformate (iv) and the action of amine on urethane (viii) were found to be most suitable in preparing the following series of urethanes and ureas respectively.

\[
\text{(II)} \quad \overset{\text{EtOH} \cdot \text{Et}_3\text{N}}{\rightleftharpoons} \quad \text{(III)}
\]

where: \( R = -\text{H, } -\text{CH}_3, -\text{OCH}_3, -\text{Cl}, -\text{Br, } -\text{C}_6\text{H}_5 \)

\[
\text{(III)} \quad + \quad \text{EtOH} \cdot \text{Et}_3\text{N} \quad \rightleftharpoons \quad \text{(IV)}
\]

where: \( R = -\text{H, } -\text{CH}_3, -\text{OCH}_3, -\text{Cl}, -\text{Br, } -\text{C}_6\text{H}_5 \)

\( R^1 = -\text{C}_6\text{H}_5, -4-\text{Cl-C}_6\text{H}_4, -4-\text{H}_2\text{CO-C}_6\text{H}_4, -4-\text{NO}_2-\text{C}_6\text{H}_4 \)

3,7-Diaryl pyrazolo[1,5-a]-1,3,5-triazine-2,4(1H)-diones (V):

3,7-Diaryl pyrazolo[1,5-a]-1,3,5-triazine-2,4(1H)-diones (V) were synthesised by base catalysed intramolecular cyclization\textsuperscript{63-65} of \( N^2\)-aryl-\( N^1\)-(5-aryl-2-carbethoxy pyrazol-3-yl)ureas (IV).

The cyclization of ureas were carried out in dry pyridine by refluxing the mixture at 140°C for 20 hours.
where: $R = -\text{H}, -\text{CH}_3, -\text{OCH}_3, -\text{Cl}, -\text{Br}, -\text{C}_6\text{H}_5$

$R^1 = -4-\text{Cl}-\text{C}_6\text{H}_4$

Physical constants of the synthesized 3-amino-5-aryl pyrazoles

(II; 1-6), ethyl-N-(5-aryl-2-carbethoxy pyrazol-3-yl) carbamates (III; 1-6),

$N^2$-aryl-$N^1$-(5-aryl-2-carbethoxy pyrazol-3-yl) ureas (IV; 1-20) and

3,7-diaryl pyrazolo[1,5-a]-1,3,5-triazine-2,4(1H)-diones (V; 1-6) are

recorded in Table-1,2,3 and 4 respectively on P.145. All the synthesized

ethyl-N-(5-aryl-2-carbethoxy pyrazol-3-yl) carbamates (III; 1-6) are

colorless to yellowish crystalline solid, soluble in dimethyl formamide,

dimethylsulfoxide and dioxane. All the $N^2$-aryl-$N^1$-(5-aryl-2-carbethoxy

pyrazol-3-yl) ureas (IV; 1-20) are colourless to yellowish crystalline

solide, soluble in dioxane, acetone, chloroform, dimethylformamide

and dimethyl sulfoxide. All the 3,7-diaryl pyrazolo[1,5-a]-1,3,5-triazine-

-2,4(1H)diones (V; 1-6) are pale yellow crystalline solids having poor

solubility in almost all organic solvents.
[B] Spectral study:

Infrared spectra:

IR spectral data of 3-amino-5-aryl pyrazoles (II)\(^{35}\) are recorded in Table-5 (p.132). The spectra showed absorption bands near 3420, 3310 and 3200 cm\(^{-1}\) due to $\nu$ NH. A strong intensity absorption near 1620 cm\(^{-1}\) has been attributed to $\delta$ NH\(_2\). Absorption bands in the region from 1600 to 1490 cm\(^{-1}\) were assigned to $\nu$ C=C and $\nu$ C=N rings.

IR spectra of ethyl-N-(5-aryl-2-carbethoxy pyrazol-3-yl)carbamates (III) (Table-6, P.134) showed medium to strong intensity band due to $\nu$ NH near 3350cm\(^{-1}\). Strong intensity absorption bands near 1745 and 1720cm\(^{-1}\) which in some cases appeared as one strong broad band were attributed to $\nu$ C=O of ester functionalities. A number of bands in the region between 1610 cm\(^{-1}\) to 1470 cm\(^{-1}\) were assigned to $\nu$ C=C and $\nu$ C=N of the rings.

Table-7, P.135 records IR spectral data of N\(^2\)-aryl-N\(^1\)(5-aryl-2-carbethoxy pyrazol-3-yl) ureas (IV). The spectra showed bands in the region 3320-3220 cm\(^{-1}\) due to $\nu$ NH. Absorption bands due to carbonyl group of ester and ureido functionalities were observed near 1710cm\(^{-1}\) which in many cases appeared as strong broad band. The region from 1625cm\(^{-1}\) to 1490cm\(^{-1}\) showed a number of absorption bands characteristic of C=C and C=N groups incorporated in the rings.

IR spectra of 3,7-diaryl pyrazolo[1,5-a]-1,3,5-triazine-2,4(1H)-diones (V) (Table-8; P.137) exhibited absorption band near 3220cm\(^{-1}\) which
was assigned to $\nu$ NH. Absorption bands due to cyclic $\nu$ C=O groups were found near 1710 and 1680 cm$^{-1}$. Absorption due to $\nu$ C=C and $\nu$ C=N (ring) occurred in the region from 1630 to 1490 cm$^{-1}$.

$^1$H NMR Spectrometry:

$^1$H NMR spectra of ethyl-N(5-aryl-2-carbethoxy pyrazol-3-yl)carbamate (1) (Table-9; P.138) taken in CDCl$_3$ showed two triplets at $\delta$ 1.35 and $\delta$ 1.51 and two quartet at $\delta$ 4.31 and 4.58 which were assigned to CH$_2$ and CH$_3$ protons respectively of two CO$_2$CH$_2$CH$_3$ functionalities. Slightly upfield triplet and quartet seems obviously due to protons of amino carbethoxy group at position-3 of the pyrazole ring. A proton at position-4 of the pyrazole ring exhibited singlet at $\delta$ 6.95 in the spectra. While NH proton showed singlet at $\delta$ 9.49 each integrated for one proton. Absorption due to aromatic protons was found in the region from $\delta$ 7.29-7.95 as multiplet.

$^1$H NMR spectral data taken in the solvent DMSO-$d_6$ of N$^2$-aryl-N$^1$-\(\text{-(5-aryl-2-carbethoxy pyrazol-3-yl) ureas (2), (3) are given in Table-9; P.138. The spectra showed triplet near $\delta$ 1.38 and a quartet near $\delta$ 4.25-4.50 due to CH$_3$ and CH$_2$ protons of CO$_2$CH$_2$CH$_3$ group respectively. A singlet near $\delta$ 6.70 was attributed to the proton at position-4 of the pyrazole ring. NH protons of the urea functionality absorbed in the region from $\delta$ 9.4 to $\delta$ 9.9 exhibiting two separate singlets. Aromatic protons were found in the region from $\delta$ 7.1 to $\delta$ 7.7 as multiplets.
$^1$H NMR spectra taken in DMSO-$d_6$ + TFA, of 3,7-diaryl pyrazolo[1,5-a]-
-1,3,5-triazine-2,4-(1H)diones (4), (5), (6) are recorded in Table-9; P.138
The spectra showed absorption signals due to CH$_3$ protons and OCH$_3$ protons
at $\delta$ 2.5 and $\delta$ 3.84 respectively as singlets. NH proton and CH proton
at position-8 of the pyrazole ring were found in the spectra as singlets
in the region near $\delta$ 9.5 and $\delta$ 6.6 respectively. Multiplets in the region
from $\delta$ 6.80 to $\delta$ 7.86 have obviously been attributed to aromatic protons.
The spectra were devoid of absorption due to CO$_2$CH$_2$CH$_3$ protons which
suggested complete cyclization of 3,7-diaryl pyrazolo[1,5-a]-1,3,5-
triazine-2,4(1H)diones.

Mass spectra :

The mass spectral fragmentation of some of the pyrazole derivatives,
3-amino-5-aryl pyrazole (II), ethyl-N-(5-aryl-2-carbethoxy pyrazol-3-yl)
carbamates (III), N$^2$-aryl-N$^1$-(5-aryl-2-carbethoxy pyrazol-3-yl) ureas (IV)
and 3,7-diaryl pyrazolo[1,5-a]-1,3,5-triazine-2,4(1H)dione were studied
under electron impact at 70 eV (Table-10; P.139).
TABLE-5: IR Spectral data of 3-Amino-5-Aryl pyrazoles (II)

![Chemical Structure]

**Characteristic IR bands (cm⁻¹)**

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>R</th>
<th>°NH</th>
<th>°NH₂, °C=C, C=N(ring)</th>
<th>°C-N, C-O</th>
<th>°Ar-H</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-H</td>
<td>3420(m)</td>
<td>1620(s) 1560(s) 1490(s) 1300(m)</td>
<td>-</td>
<td>760(s) 690(s)</td>
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<tr>
<td></td>
<td></td>
<td>3310(m)</td>
<td>1580(m) 1510(s) 1470(s) 1280(w)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3200(m)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>-CH₃</td>
<td>3425(m)</td>
<td>1620(s) 1570(m) 1510(m) 1310(m)</td>
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<td>820(s)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3380(m)</td>
<td>1600(m) 1560(m) 1500(m) 1270(m)</td>
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<tr>
<td></td>
<td></td>
<td>3205(m)</td>
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<tr>
<td>3</td>
<td>-OCH₃</td>
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<td>1620(s) 1560(m) 1510(s) 1305(m)</td>
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<td>815(s)</td>
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<td></td>
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<td>3380(m)</td>
<td>1600(s) 1555(m) 1500(s) 1270(m)</td>
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<tr>
<td></td>
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<td>3320(m)</td>
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<tr>
<td></td>
<td></td>
<td>3210(m)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compd. No.</td>
<td>R</td>
<td>$\nu$ NH</td>
<td>$\delta$ NH$_2$, $\nu$ C=C, C=N (ring)</td>
<td>$\nu$ C-N, C-O</td>
<td>$\delta$ Ar-H</td>
</tr>
<tr>
<td>-----------</td>
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<td></td>
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<td>3200 (m)</td>
<td></td>
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</tr>
<tr>
<td>6</td>
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<td>1310 (m)</td>
<td>820 (s)</td>
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<td>1280 (m)</td>
<td>765 (s)</td>
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<td></td>
<td></td>
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<td>690 (s)</td>
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<td>( \nu_{C-N} )</td>
<td>( \delta_{C=O} )</td>
<td>( \delta_{NH} )</td>
</tr>
<tr>
<td>------------</td>
<td>-----------</td>
<td>----------------</td>
<td>----------------</td>
<td>-----------------</td>
<td>----------------</td>
</tr>
<tr>
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<td>1600 (m)</td>
<td>-</td>
<td>3340 (m)</td>
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<tr>
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<td>-CH₃</td>
<td>1720 (s)</td>
<td>1570 (m)</td>
<td>-</td>
<td>3360 (s)</td>
</tr>
<tr>
<td>3</td>
<td>-OCH₃</td>
<td>1740 (s)</td>
<td>1590 (s)</td>
<td>-</td>
<td>3350 (m)</td>
</tr>
<tr>
<td>4</td>
<td>-Cl</td>
<td>1720 (s)</td>
<td>1590 (s)</td>
<td>-</td>
<td>3345 (s)</td>
</tr>
<tr>
<td>5</td>
<td>-Br</td>
<td>1740 (s)</td>
<td>1590 (s)</td>
<td>-</td>
<td>3345 (s)</td>
</tr>
<tr>
<td>6</td>
<td>-C₆H₅</td>
<td>1745 (s)</td>
<td>1590 (s)</td>
<td>-</td>
<td>3350 (s)</td>
</tr>
</tbody>
</table>

**Table 6: IR Spectral data of Ethyl-N-(5-Aryl)-2-carbethoxy Pyrazol-3-yl)-Carbamates (III)**
TABLE 7: IR Spectral data of N^2-ary1-N^1-(5-aryl-2-carbethoxy pyrazol-3-yl)Ureas (IV)

![Chemical Structure]

**Characteristic IR bands (cm⁻¹)**

<table>
<thead>
<tr>
<th>Compd No.</th>
<th>R</th>
<th>R¹</th>
<th>v NH</th>
<th>v C=O</th>
<th>v C=C, C=N (ring)</th>
<th>v C-N, C-O</th>
<th>v Ar-H</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-H</td>
<td>-4-H_3CO-C_6H_4</td>
<td>3270(s)</td>
<td>1710(s)</td>
<td>1625(s)</td>
<td>1580(s)</td>
<td>1510(s)</td>
</tr>
<tr>
<td>2</td>
<td>-H</td>
<td>-4-Cl-C_6H_4</td>
<td>3300(s)</td>
<td>1710(s)</td>
<td>1610(s)</td>
<td>1570(s)</td>
<td>1500(s)</td>
</tr>
<tr>
<td>3</td>
<td>-OCH_3</td>
<td>-4-Cl-C_6H_4</td>
<td>3305(s)</td>
<td>1720(s)</td>
<td>1610(s)</td>
<td>1570(s)</td>
<td>1500(s)</td>
</tr>
<tr>
<td>4</td>
<td>-Cl</td>
<td>-C_6H_5</td>
<td>3300(s)</td>
<td>1720(s)</td>
<td>1610(s)</td>
<td>1575(s)</td>
<td>1510(s)</td>
</tr>
<tr>
<td>5</td>
<td>-Cl</td>
<td>-4-CH_3-C_6H_4</td>
<td>3300(s)</td>
<td>1720(s)</td>
<td>1620(s)</td>
<td>1570(s)</td>
<td>1530(s)</td>
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</tbody>
</table>

135
<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>R</th>
<th>$R^1$</th>
<th>$\nu \text{NH}$</th>
<th>$\nu \text{C=O}$</th>
<th>$\nu \text{C=C, C=N\text{(ring)}}$</th>
<th>$\nu \text{C-N, C-O}$</th>
<th>$\delta \text{Ar-H}$</th>
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<tbody>
<tr>
<td>6</td>
<td>-C1</td>
<td>-4-C1-C$_6$H$_4$-</td>
<td>3300 (s)</td>
<td>1710 (s)</td>
<td>1610 (s)</td>
<td>1570 (m)</td>
<td>1500 (s)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3220 (s)</td>
<td></td>
<td>1590 (s)</td>
<td>1555 (s)</td>
<td>1490 (s)</td>
<td>1300 (s)</td>
</tr>
<tr>
<td>7</td>
<td>-C1</td>
<td>-4-C$_6$H$_4$-</td>
<td>3320 (s)</td>
<td>1710 (s)</td>
<td>1610 (s)</td>
<td>1590 (s)</td>
<td>1500 (s)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3220 (s)</td>
<td></td>
<td>1590 (s)</td>
<td>1550 (s)</td>
<td>1490 (s)</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>-C1</td>
<td>-4-C$_5$H$_5$-C$_6$H$_4$</td>
<td>3305 (s)</td>
<td>1710 (s)</td>
<td>1625 (s)</td>
<td>1580 (s)</td>
<td>1510 (w)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3230 (s)</td>
<td></td>
<td>1590 (s)</td>
<td>1555 (s)</td>
<td>1490 (s)</td>
<td>1280 (s)</td>
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### TABLE-8: IR Spectra data of 3,7-Diaryl Pyrazolo[1,5-a]-1,3,5-triazine-2,4(1H) diones (V)

![Chemical Structure](image)

**Characteristic IR bands (cm⁻¹)**

<table>
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<tr>
<th>Compd. No.</th>
<th>R</th>
<th>R¹</th>
<th>ν NH</th>
<th>ν C=O</th>
<th>ν C=C, C=N</th>
<th>ν C=N</th>
<th>δ Ar-H</th>
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</thead>
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<tr>
<td>1</td>
<td>-H</td>
<td>-4-Cl-C₆H₄</td>
<td>3220 (m)</td>
<td>1710 (s)</td>
<td>1630 (m)</td>
<td>1565 (s)</td>
<td>1280 (s)</td>
</tr>
<tr>
<td>2</td>
<td>-CH₃</td>
<td>-4-Cl-C₆H₄</td>
<td>3210 (m)</td>
<td>1715 (s)</td>
<td>1625 (m)</td>
<td>1560 (s)</td>
<td>1285 (s)</td>
</tr>
<tr>
<td>3</td>
<td>-Br</td>
<td>-4-Cl-C₆H₄</td>
<td>3210 (m)</td>
<td>1710 (s)</td>
<td>1630 (m)</td>
<td>1570 (s)</td>
<td>1280 (s)</td>
</tr>
<tr>
<td>No.</td>
<td>Compound</td>
<td>Characteristic $^1$H NMR signals (δ ppm) at 60 MHz</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----</td>
<td>----------</td>
<td>-------------------------------------------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td><img src="image1" alt="Structure 1" /></td>
<td>1.35 (t, 3H, (-\text{CO}_2\text{CH}_2\text{CH}_3)); 1.51 (t, 3H, (\text{CO}_2\text{CH}_2\text{CH}_3)); 4.31 (q, 2H, (-\text{CO}_2\text{CH}_2\text{CH}_3)); 4.58 (q, 2H, (-\text{CO}_2\text{CH}_2\text{CH}_3)); 6.95 (s, 1H, CH); 7.29-7.95 (m, 4H, Ar-H); 9.49 (s, 1H, NH)</td>
<td></td>
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<tr>
<td>2</td>
<td><img src="image2" alt="Structure 2" /></td>
<td>1.38 (t, 3H, (-\text{CO}_2\text{CH}_2\text{CH}_3)); 2.35 (s, 3H, CH3); 4.25 (q, 2H, (-\text{CO}_2\text{CH}_2\text{CH}_3)); 6.70 (s, 1H, CH); 7.12-7.70 (m, 8H, Ar-H); 9.40 (s, 1H, NH); 9.86 (s, 1H, NH)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>3</td>
<td><img src="image3" alt="Structure 3" /></td>
<td>1.38 (t, 3H, (-\text{CO}_2\text{CH}_2\text{CH}_3)); 4.50 (q, 2H, (-\text{CO}_2\text{CH}_2\text{CH}_3)); 6.67 (s, 1H, CH); 7.32-7.66 (m, 8H, Ar-H); 9.60 (s, 1H, NH); 9.86 (s, 1H, NH)</td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>4</td>
<td><img src="image4" alt="Structure 4" /></td>
<td>2.50 (s, 3H, CH3); 6.55 (s, 1H, CH); 6.85-7.85 (m, 8H, Ar-H); 9.4 (s, 1H, NH)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td><img src="image5" alt="Structure 5" /></td>
<td>3.84 (s, 3H, OCH3); 6.52 (s, 1H, CH); 6.84-7.74 (m, 8H, Ar-H); 9.66 (s, 1H, NH)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td><img src="image6" alt="Structure 6" /></td>
<td>6.66 (s, 1H, CH); 7.35-7.86 (m, 8H, Ar-H); 9.36 (s, 1H, NH)</td>
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</table>

* s=singlet; m=multiplet; t=triplet; d=doublet, q=quartet.
TABLE-10: Mass spectral data of pyrazole derivatives

<table>
<thead>
<tr>
<th>No.</th>
<th>Compound</th>
<th>m/e *Base peak, M = Molecularion Peak</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Structure" /></td>
<td>196,195,194,193(M)*, 166,165,164,162,158,139,138,137,136,130, 127,116,103,102,101,97,89,77,76,75.</td>
</tr>
<tr>
<td>4</td>
<td><img src="image4" alt="Structure" /></td>
<td>380(M), 393,352,262,261*,233,216,215,202,200,189,174,161,160.</td>
</tr>
<tr>
<td>5</td>
<td><img src="image5" alt="Structure" /></td>
<td>427,426(M), 424,423,262,261*,219,205,204,192,190,177,176,165,154 153,131,130,102.</td>
</tr>
<tr>
<td>6</td>
<td><img src="image6" alt="Structure" /></td>
<td>463,462(M),461,312,311*,310,265,263,252,250,240,239,238,237,208 183,182,157,130.</td>
</tr>
<tr>
<td>7</td>
<td><img src="image7" alt="Structure" /></td>
<td>417,416(M),415,402,362,360,341,339,327,313,311,265,263,239,237*, 208,131,130,129,128,102,100.</td>
</tr>
</tbody>
</table>
Synthesis of 3-amino-5-aryl pyrazoles (II): \(^{33,34}\)

To a solution of hydrazine hydrate (0.2 mole) in water (50 ml), a mixture of \(\beta\)-chlorocinnamonic nitrile (0.1 mole) and ethanol (50ml) was added at once. The resulting mixture was refluxed for 5 hours, cooled and diluted with cold water (200ml). The product separated was filtered and crystallised from water, n-butanol or dimethyl formamide.

3-Amino-5-(4-tolyl)pyrazole (II;2):

To a solution of hydrazine hydrate (80%) (10ml; 0.2 mole) in water (50ml) a mixture of \(\beta\)-chlorocinnamic nitrile [\(\beta\)-chloro-\(\beta\)-(4-tolyl)acrylonitrile] (I; 17.75g; 0.1 mole) and ethanol (50ml) was added at once. The resulting mixture was refluxed for 5 hours, cooled and diluted with cold water (200ml). The product separated was filtered, washed with (3x10 ml) water and dried. It was crystallized from hot water; yield; 12.8g (74%) colorless flakes, m.p. 147-150\(^\circ\)C.

3-Amino-5-(4-chlorophenyl)pyrazole (II;4):

To a solution of hydrazine hydrate (80%) (10ml; 0.2 mole) in water (50ml) a mixture of \(\beta\)-chlorocinnamic nitrile [\(\beta\)-chloro-\(\beta\)-(4-chlorophenyl)acrylonitrile] (I; 19.7g; 0.1 mole) and ethanol (50ml) was added at once. The resulting mixture was refluxed for 5 hours, cooled and diluted with cold water (200ml). The product separated was filtered washed with (3x10ml) water and dried. It was crystallized from hot water; yield 16.25g (84%) colorless flakes, m.p. 173-175\(^\circ\)C.

Various pyrazoles, thus prepared are listed in Table-1; P.145.
Synthesis of ethyl-N-[(5-aryl-2-carbethoxy pyrazol-3-yl)carbamates (III):

3-Amino-5-aryl pyrazole was mixed intimately with excess of ethyl chloroformate and the mixture heated gradually to 120°. This temperature was maintained for 4 hours, followed by removal of the unchanged ethyl chloroformate under reduced pressure. On crystallisation from ethanol, the residue gave the pure product.

Ethyl-N-(5-phenyl-2-carbethoxy pyrazol-3-yl)carbamate (III;1):

3-Amino-5-phenyl pyrazole (II;1) (15.9g; 0.1 mole) was mixed intimately with excess of ethyl chloroformate (30ml; 0.3 mole) and the mixture was heated gradually to 120°. This temperature was maintained for 4 hours, followed by removal of the unchanged ethyl chloroformate under reduced pressure. Crystallization of crude product from ethanol afforded 23g (75%) colorless needles, m.p. 116-119°C.

TLC ; Rf = 5.5; Benzene : Isopropanol (4:1)

Ethyl-N-[(5-(4-bromophenyl)-2-carbethoxy pyrazol-3-yl)carbamate (III;5):

3-Amino-5-(4-bromophenyl)pyrazole (II;5) (23.8g; 0.1 mole) was mixed intimately with excess of ethyl chloroformate (30ml; 0.3 mole) and the mixture was heated gradually to 120°. This temperature was maintained for 5 hours, followed by removal of the unchanged ethyl chloroformate under reduced pressure. Crystallization of crude product from ethanol afforded 32.5g (85%) cream colored needles, m.p. 110-111°C.

TLC ; Rf = 5.7; Benzene : Isopropanol (4:1)

Various carbamates, thus prepared are listed in Table-2; P.146.
N^2-(5-aryl-2-carbethoxy pyrazol-3-yl) urea (IV; 1):  

To an equimolecular mixture of ethyl-N-(5-aryl-2-carbethoxy pyrazol-3-yl) carbamate (0.02 mole) and 4-substituted aniline (0.02 mole) in 100ml ethanol, was added 4ml triethylamine. The resulting mixture was refluxed on steam bath for 9 hours, the solvent distilled off under reduced pressure and the residue was washed with cold ethanol and toluene, and crystallized from ethanol to get title compounds (Table-3); P.147.

N^2-(4-Chlorobenzyl)-N^1-(5-phenyl-2-carbethoxy pyrazol-3-yl) urea (IV; 1):  

To an equimolecular mixture of ethyl-N-(5-phenyl-2-carbethoxy pyrazol-3-yl) carbamate (II; 1) (6.06g; 0.02 mole) and 4-chloroaniline (2.55g; 0.02 mole) in 100ml ethanol, 4ml triethylamine was added. The resulting mixture was refluxed on steam bath for 7 hours and the solvent was distilled off under reduced pressure. The residue was washed successively with cold ethanol (5ml) and toluene (8ml). Crystallization from ethanol yielded 5.2g (65%) colorless flakes, m.p. 180-181°C.  

TLC; Rf = 7.9; Benzene : Ethylacetate (4.5:1.5).

N^2-(4-Nitrophenyl)-N^1-(5-phenyl-2-carbethoxy pyrazol-3-yl) urea (IV; 4):  

To an equimolecular mixture of ethyl-N-(5-phenyl-2-carbethoxy pyrazol-3-yl) carbamate (II; 1) (6.06g; 0.02mole) and 4-nitroaniline (2.76g; 0.02 mole) in ethanol (100ml), 4 ml triethylamine was added. The resulting mixture was refluxed on steam bath for 9 hours and the solvent was distilled off under reduced pressure. The residue was washed successively with cold ethanol (2 to 4ml) and toluene (10ml). Crystallization from ethanol yielded 5.53g (70%) yellowish flakes, m.p. 100-101°C.  

TLC; Rf = 7.8 ; Benzene ; Ethylacetate (4.5 : 1.5)
Synthesis of 3,7-diaryl pyrazolo[1,5-a]-1,3,5-triazine-2,4-(1H)-diones (V):

A mixture of N^2-aryl-N^1-(5-aryl-2-carbethoxy pyrazol-3-yl)urea (IV) (0.02 mole) and dry pyridine (75ml) was refluxed at 140°. This temperature was maintained for 20 hours. The reaction mixture was cooled and acidified to pH-2 by the addition of 50% hydrochloric acid. The separated product was filtered, washed with water, ethanol and dried. Crystallization from a mixture of dimethylformamide and water or acetic acid afforded pure product (Table-4); P.149

3-(4-Chlorophenyl)-7-phenyl pyrazolo[1,5-a]-1,3,5-triazine-2,4-(1H)-diones (V;1):

A mixture of N^2-(4-chlorophenyl)-N^1-(5-phenyl-2-carbethoxy pyrazol-3-yl)urea (IV;1) (7.69g; 0.02 mole) and dry pyridine (75ml) was refluxed at 140°. This temperature was maintained for 15 to 16 hours. Reaction mixture was then cooled and acidified to pH-2 by addition of 50% hydrochloric acid. The product separated, was filtered, washed successively with water (10ml), ethanol (10ml) and dried. Crystallization from acetic acid afforded 5.4g (80%) yellowish flakes, m.p. 324-26°C.

TLC; Rf = 6.3 ; Benzene : Ethylacetate (4.5 : 1.5)

3,7-Bis(4-chlorophenyl)pyrazolo[1,5-a]-1,3,5-triazine-2,4(1H)-dione (V;4):

A mixture of N^2-(4-chlorophenyl)-N^1-[5-(4-chlorophenyl)-2-carbethoxy pyrazol-3-yl]urea (IV;12) (8.36g; 0.02 mole) and dry pyridine (75 ml) was refluxed at 140°. This temperature was maintained for 20 hours. Reaction mixture was then cooled and acidified to pH-2 by addition of 50% hydrochloric
acid. The product was filtered, washed successively with water (10ml), ethanol (10ml) and dried. Crystallization from DMF-water mixture yielded 5.6g (76%) pale yellow flakes, m.p. 330-340° C.

TLC; Rf = 6.5; Benzene : Ethylacetate (4.5 : 1.5)


<table>
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</thead>
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<td>Calcd.</td>
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<td>1</td>
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<td>126-7</td>
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<td>C_{9}H_{9}N_{3}</td>
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<td>(159)</td>
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<tr>
<td>2</td>
<td>CH_{3}-</td>
<td>147-50</td>
<td>75</td>
<td>C_{10}H_{11}N_{3}</td>
<td>24.28</td>
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<td>(173)</td>
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</tr>
<tr>
<td>3</td>
<td>OCH_{3}-</td>
<td>141-43</td>
<td>70</td>
<td>C_{10}H_{11}N_{3}O</td>
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<td>(189)</td>
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<tr>
<td>4</td>
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<td>(193.5)</td>
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<td>Br-</td>
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<td>C_{9}H_{8}BrN_{3}</td>
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<td>(238)</td>
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<td>(235)</td>
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TABLE 2: Physical Constants of Ethyl-N-(5-Aryl-2-Carbethoxy-Pyrazol-3-yl)Carbamates (III)

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<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>116-19 (EtOH)</td>
<td>75</td>
<td>C_{15}H_{17}N_{5}O_{4} (303)</td>
<td>13.86</td>
<td>13.80</td>
<td>59.41</td>
<td>59.48</td>
<td>5.61</td>
<td>5.53</td>
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</tr>
<tr>
<td>2</td>
<td>CH\textsubscript{3}</td>
<td>134-36 (EtOH)</td>
<td>80</td>
<td>C_{16}H_{19}N_{3}O_{4} (317)</td>
<td>13.25</td>
<td>13.15</td>
<td>60.57</td>
<td>60.49</td>
<td>5.99</td>
<td>5.89</td>
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<tr>
<td>3</td>
<td>OCH\textsubscript{3}</td>
<td>110-12 (EtOH)</td>
<td>83</td>
<td>C_{16}H_{19}N_{3}O_{5} (333)</td>
<td>12.61</td>
<td>12.65</td>
<td>57.66</td>
<td>57.61</td>
<td>5.70</td>
<td>5.68</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Cl</td>
<td>121-23 (EtOH)</td>
<td>72</td>
<td>C_{15}H_{16}ClN_{3}O_{4} (337.5)</td>
<td>12.44</td>
<td>12.39</td>
<td>53.33</td>
<td>53.46</td>
<td>4.74</td>
<td>4.79</td>
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<tr>
<td>5</td>
<td>Br</td>
<td>110-11 (EtOH)</td>
<td>85</td>
<td>C_{15}H_{16}BrN_{3}O_{4} (382)</td>
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<td>11.04</td>
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<td>47.18</td>
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<td>4.21</td>
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<td>6</td>
<td>C\textsubscript{6}H\textsubscript{5}</td>
<td>141-42 (EtOH)</td>
<td>70</td>
<td>C_{21}H_{21}N_{3}O_{4} (379)</td>
<td>11.08</td>
<td>11.01</td>
<td>66.49</td>
<td>66.38</td>
<td>4.54</td>
<td>4.57</td>
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TABLE 3: \( N^2 \)-Aryl-\( N^1 \)-(5-Aryl-2-Carbethoxy Pyrazol-3-yl) Urea (IV)

\[
\text{NH} - \text{CO} - \text{NH} - R^1
\]

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<td>4-Cl-C(_6)H(_4)-</td>
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<td>C(<em>{19})H(</em>{17})ClN(_4)O(_3)</td>
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<td>C(<em>{20})H(</em>{20})N(_4)O(_4)</td>
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<td>14.79</td>
<td>63.16</td>
<td>63.20</td>
<td>4.17</td>
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<td>H-</td>
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<td>184-85</td>
<td>C(<em>{19})H(</em>{18})N(_4)O(_3)</td>
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<td>70.42</td>
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TABLE 4: Physical Constants of 3,7-Diaryl Pyrazolo[1,5-a]-1,3,5-triazine-2,4(1H)diones (V)

![Chemical Structure](image)

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<th>Compd. No.</th>
<th>R</th>
<th>R&lt;sup&gt;1&lt;/sup&gt;</th>
<th>m.p. °C</th>
<th>Mol. Formula</th>
<th>Nitrogen</th>
<th>Carbon</th>
<th>Hydrogen</th>
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<td>Found</td>
<td>Calcd.</td>
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<td>4-Cl-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;-</td>
<td>324-26</td>
<td>C&lt;sub&gt;17&lt;/sub&gt;H&lt;sub&gt;11&lt;/sub&gt;C&lt;sub&gt;1&lt;/sub&gt;N&lt;sub&gt;4&lt;/sub&gt;O&lt;sub&gt;2&lt;/sub&gt;</td>
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<td>13.57</td>
<td>66.59</td>
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</table>
REFERENCES

1. Knorr, Ber., 16, 2597 (1883); Ger. Patent, 26,429 (1883).

2. Knorr, Ber., 17, 546, 2032 (1884).


