Synthesis and Reactions of Some β-Aroyl-α -(indol-3-yl)-Propionic Acids

G.H.SAYED[+],M.Y.EL-KADY,I.ABD-ELMAWGOUD[++] AND M.HAMDY

[++]*Chemistry Department,Faculty of Science, Ain Shams University,Abbassia,Cairo,Egypt.*

(Received 12th January, 1983, Revised 9th October, 1983)

Summary: β -Aroyl- α -(indol-3-yl)propionic acids 2 were prepared by the reaction of β -aroylacrylic acid 1 with indoles in dry benzene. Condensation of 2 with anisaldehyde afforded the β -arylidene derivatives 3. Dehydration of 2 yielded the butenolides 4 which underwent ring opening by reaction with amines to give 5. Reaction of 2 with hydrazine hydrate and phenylhydrazine afforded the corresponding dihydropyridazinones 6a-d and 7a-d. Dihydropyridazinones 6 reacted with dimethylsulfate, diethylsulfate, ethyl bromoacetate, $POCl_3$ and P_2S_5 and yielded the corresponding N-alkylated, chloropyridazine and thione derivatives 8a-c, 13a, 13b, 17a and 17b. Reactions of pyridazinones 6 with anisaldehyde, Grignard reagents and bromine-acetic acid mixture are described. The behaviour of 3-chloropyridazine 13 towards hydrazine hydrate, sodium azide and anthranilic acid was investigated. Carboethoxymethylation and the action of p-anisidine and Grignard reagents on the thione 17 were investigated.

A large number of pyridazinones are reported to exhibit insecticidal [1,2], allergenic [3], anti-hypertensive [4,5], analgesic [6], antiinflammatory and bactericidal [7] activities. This prompted us to synthesize new dihydropyridazinones through the nucleophilic addition of indoles to β -aroylacrylic acids followed by cyclization of the adducts to the corresponding dihydropyridazinones.

The reaction of p-chloro-(1a) or 3-methyl-4-chloro-(1b)- β -benzoylacrylic acids with indole or 1,2-dimethylindole in dry benzene gave β-aroyl- α -(indol-3-yl)propionic acids 2a-d. The structure of the acids 2a-d was derived from their spectral data. Their IR showed bands at 1730-1690 cm^{-1} and 1690-1680 cm^{-1} attributable to the carbonyl groups of acid and ketone, respectively. The UV spectrum of 2a showed a λ_{max} at 248. The ^1H-n.m.r. spectrum of 2a in $CDCl_3$ showed the following signals: 8.15-7.12 (10 H, m, ArH + NH-CH), 4.71-3.24 (3H, m, CH_2-CH) and that of 2b showed signals at 8-7 (8H, m, ArH), 4.65-3 (3H, m, CH_2CH), 3.65 (3H, s, CH_3), 2.5 (3H, s, CH_3). The mass spectrum* of 2b exhibited peaks at m/z 355 (22.3 %). 310 (9.6%), 202 (41.8%), 171 (17.2%), 158 (100%), 145 (7.1%), 139 (10.73%) and 111 (6.1%).

The β-aroyl-α-(indol-3-yl)propionic acid 2c was condensed with p-chlorobenzaldehyde and p-nitrobenzaldehyde in boiling ethanol with a few drops of piperidine to give the corresponding α(indole-3-yl)- β-arylidene- β-aroylpropionic acids 3a and 3b. The infrared spectra of 3 exhibited two νCO

*IR ν_{max} here and elsewhere in the paper cm^{-1} m/z here and elsewhere in the paper were calculated for the isotope ^{35}Cl.

bands in the region 1675-1670 cm^{-1} and 1720-1710 cm^{-1}, indicating the presence of ketone carbonyl and carboxyl group, respectively.

The propionic acid derivatives 2a and 2c were easily dehydrated by boiling with acetic anhydride or heating at their melting point, to yield α(indol-3-yl)- γ-aroyl-$\Delta^{\beta\gamma}$-butenolides 4a and 4b, respectively. The structures of 4 were established from the following findings:-

a)The IR spectra of 4a show strong absorption at 1760 cm^{-1} characteristic of five-membered lactone and the band for conjugated C=C at 1645 cm^{-1}[8].

b) They are readily hydrolysed by hot alkali giving the corresponding acids 2.

c) Compound 4b reacts with ethanolamine and benzylamine in boiling ethanol to give α-(indol-3-yl)- β-(3-methyl-4-chloro)-benozyl propionic acid-N-alklylamide 5a and 5b. The IR spectra of 5 showed absorption bands at 1685-1675 cm^{-1}(ν C=O) and at 3340-3190 cm^{-1} (νNH). The condensation of acids 2a-d with hydrazine hydrate or phenylhydrazine yielded the corresponding 4,6-disubstituted 4,5-dihydropyridazin-3-ones (6a-d) and 2,4,6-trisubstituted-4,5 dihydro pyridazin-3-ones (7a-d) respectively. The structure of 6a-d and 7a-d were established on the basis of their elemental analysis and spectral data. Their IR spectra showed a band at 1695-1660 cm^{-1}characteristic of the C=O of cyclic amides. The UV spectrum of 7c showed a λ_{max} at 288. The ^{1}H-n.m.r. spectrum of 6a in deuterated acetone exhibited signals at 7.9-7 (10 H, m, ArH + NHCH), 4.12 (t, CH), 3.38 (d, CH_2) and that of 7a showed singals at 8.1 - 7.1 (15 H, m, ArH + NHCH), 4.5 (t, CH), 3.67 (d, CH_2). The mass spectrum of 6a showed peaks at m/z 323 (46.8%), 295 (1.5%), 157 (100%), 143 (20.0%), 129 (30.5%) and 117 (7.23%) and that of 7a showed peaks at m/z 399 (100%), 371 (35.2%), 280 (12.4%), 157 (34.6%), 143 (28.3%), 129 (14.6%), 119 (1.36%), 117 (8.31%), 91 (52.36%), 77 (11.52%) 64 (9.07%) and 51 (3.85%).

Alkylation of 6c with dimethylsulfate, diethylsulfate or ethyl bromoacetate gave the N-alkylated compounds 8a-c. The IR spectra of 8 showed a band at 1675-1645 cm^{-1} characteristic of the C=O of cyclic amides; an additional band at 1740 for 8c attributable to C=O of carboxylic ester.

Condensation of 6a with anisaldehyde in the presence of ethanolic KOH took place at the 5-position [9], to give 4,5,6-trisubstituted pyridazin-3-one 9. The IR spectrum of 9 showed the C=O of cyclic amide at 1665 cm^{-1}.

It is reported that dihydropyridazinone undergoes dehydrogenation upon treatment with bromine and acetic acid [10]. A similar dehydrogenation of the dihydropyridazinones 6a and 6c with bromine-acetic acid mixture afforded the pyridazinones (10a and 10b).

The IR spectra showed bands due to cyclic amide C=O (1645 cm^{-1}), C=N (1600 cm^{-1}) and NH (3400-3260 cm^{-1}).

Reaction between phenylmagnesium bromide and the pyridazinone 10b gave the dihydropyridazinone 11 by 1,4-addition to the -C=C-C=N- system. This is in accordance with the result obtained by Kaddah et al. [11]. The IR spectrum of 11 showed bands at 1645, 1595 and 3420 cm^{-1} attributable to C=O, C=N and NH groups, respec-

tively. The ^{1}H-n.m.r. spectrum of 11 in $CDCl_3$ showed the following signals: 8.2-7.1 (14 H, m, ArH + NH-CH), 4.4 (2 H,s,CH_2), 2.3 (3 H, s, CH_3).

Reaction of 6c with p-methoxyphenylmagnesium bromide gave the 3,4,6-trisubstituted pyridazine (12) formed by 1,2-addition to the carbonyl group followed by elimination of a molecule of water and subsequent spontaneous dehydrogenation. Its IR spectrum was devoid of ν C=O vibrations. This is in accordance with the result obtained by Fateen et al. [12]. The ^{1}H-n.m.r. spectrum of 12 in $CDCl_3$ showed the following signals: 7.9-6.7 (13 H, m, ArH + NH-CH), 4.2 (1 H, s,CH), 3.7 (3H,s,CH_3O-), 2.3 (3H, s,CH_3).

Treatment of 6a and 6c with $POCl_3$ gave 3-chloro-4-(indol-3-yl)-6-aryl-4,5-dihydropyridazine 13a and 13b. Their IR were devoid of C=O vibrations. In this investigation, the behaviour of the 3-chloropyridazine 13 towards different reagents has also been described.

Reaction of 13a with sodium azide in dimethylformamide under reflux gave the tetrazolopyridazine 14. The IR absorption spectrum [13], showed absorption bands at 1015 and 1095 characteristic of the tetrazole ring and at 1630 cm^{-1} attributable to ν C=N.

Anthranilic acid reacted with 13a at 150° to give the quinazolinone derivative 15. Its IR spectrum showed a band at 1700 (C=O) [14] and 1630 cm^{-1} (C=N).

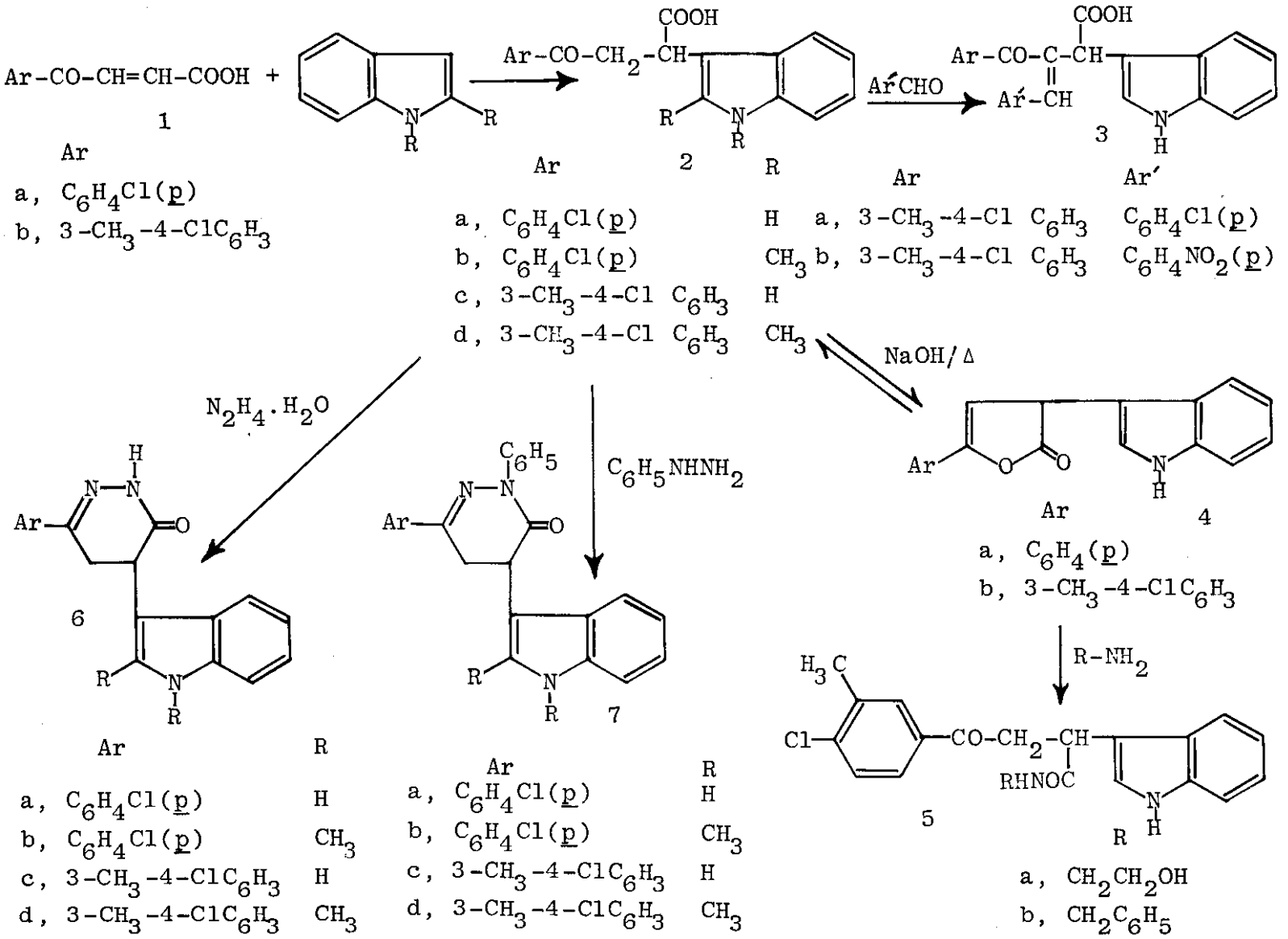
The 3-chloropyridazine 13b reacted with hydrazine hydrate in absolute ethanol to give 3-hydrazino-4-(indol-3-yl)-6-aryl-4,5-dihydropyridazine 16.

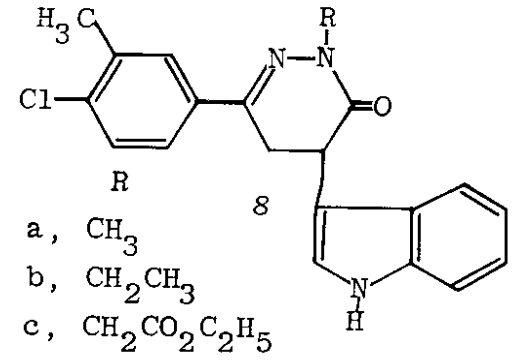
The 4,6-disubsituted 4,5-dihydropyridazin-3-ones 6a and 6c react with phosphorus pentasulfide in dry xylene to give the corresponding pyridazine thione (17a and 17b), a reaction in which thionation together with dehydrogenation takes place. This is in accordance with our previous results [15]. The infrared spectra of 17 exhibited characteristic absorption bands for ν(N-C=S) at 1475-1470 cm^{-1}, ν (C=S)at 1380 cm^{-1} and ν(NH) at 3460-3440 cm^{-1}. The ^{1}H-n.m.r. spectrum of 17a in $CDCl_3$ showed the following signal 7.9-7.2 (10 H,m,ArH + NHCH), 6.9 (1H,s, proton of pyridazine nucleus), 4.6 (1H, s, NH).

Reaction of 17a with p-anisidine yielded Schiff bases 18 which shows IR absorption bands at 1670 and 1620 for ν C=N and 3480 cm^{-1} due to ν NH.

The present investigation also deals with carboethyoxymethylation of the thiopyridazinone 17a. Treatment of 17a with ethyl bromoacetate in dry acetone yielded the corresponding 3-alkylthiopyridazine derivative 19. The IR absorption spectrum of 19 shows absorption bands at 1640 due toν(C=N) and at 1730 cm^{-1} attributable toν(C=O) of carbocyclic ester.

A study of the reaction of pyridazinethione 17b with phenylmagnesium bromide was also undertaken. When 17b was treated with phenylmagnesium bromide 6-(3-methyl-4-chloro-phenyl)-4-(indol-3-yl)-4-phenyl 4,5-dihydropyridazin-3-thione 20 was formed. The reaction takes place by 1,4-addition of phenylmagnesium bromide to the unsaturated C=N. This is in accordance with our previous results [15]. The IR absorption spectrum of 20 reveals the NH stretching frequency in the region of 3420 cm^{-1} and ν(C=S)


Ar-CO-CH=CH-COOH + 1
Ar
a, C6H4Cl(p)
b, 3-CH3-4-ClC6H3
Ar-CO-CH2-CH
COOH
R
N
R
2
Ar
R
a, C6H4Cl(p) H
b, C6H4Cl(p) CH3
c, 3-CH3-4-Cl C6H3 H
d, 3-CH3-4-Cl C6H3 CH3
ArCHO
Ar-CO-C-CH
Ar-CH
3
Ar
Ar'
a, 3-CH3-4-Cl C6H3 C6H4Cl(p)
b, 3-CH3-4-Cl C6H3 C6H4NO2(p)
N2H4.H2O
C6H5NHNH2
NaOH/Δ
Ar
O
6
Ar
R
a, C6H4Cl(p) H
b, C6H4Cl(p) CH3
c, 3-CH3-4-ClC6H3 H
d, 3-CH3-4-ClC6H3 CH3
C6H5
7
Ar
R
a, C6H4Cl(p) H
b, C6H4Cl(p) CH3
c, 3-CH3-4-ClC6H3 H
d, 3-CH3-4-ClC6H3 CH3
4
Ar
a, C6H4(p)
b, 3-CH3-4-ClC6H3
R-NH2
H3C
Cl
CO-CH2-CH
RHNOC
5
R
a, CH2CH2OH
b, CH2C6H5



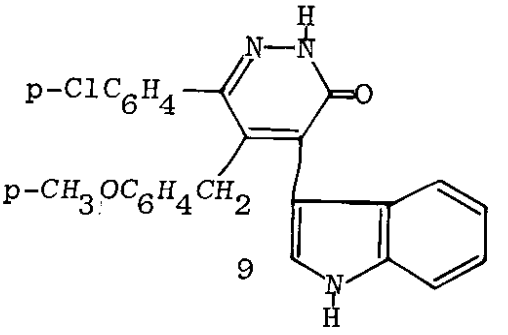
R

a, CH_3

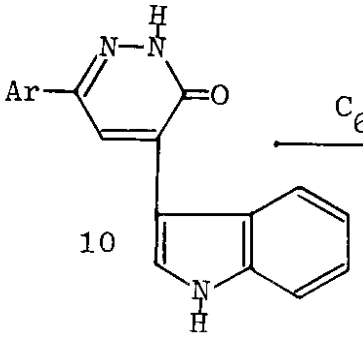
b, CH_2CH_3

c, $CH_2CO_2C_2H_5$

8



9



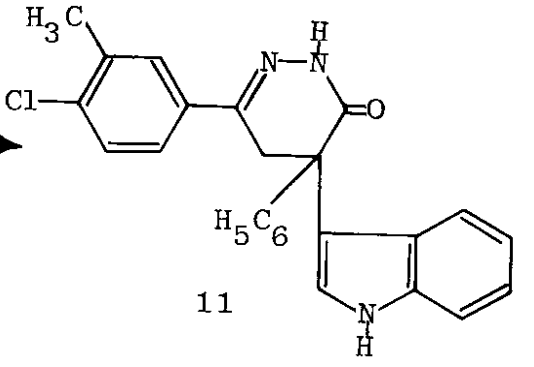
10

Ar

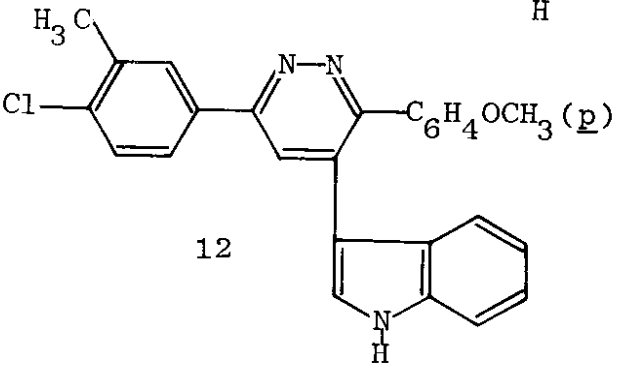
a, $C_6H_4Cl(p)$

b, $3\text{-}CH_3\text{-}4\text{-}ClC_6H_3$

C_6H_5MgBr



11



12

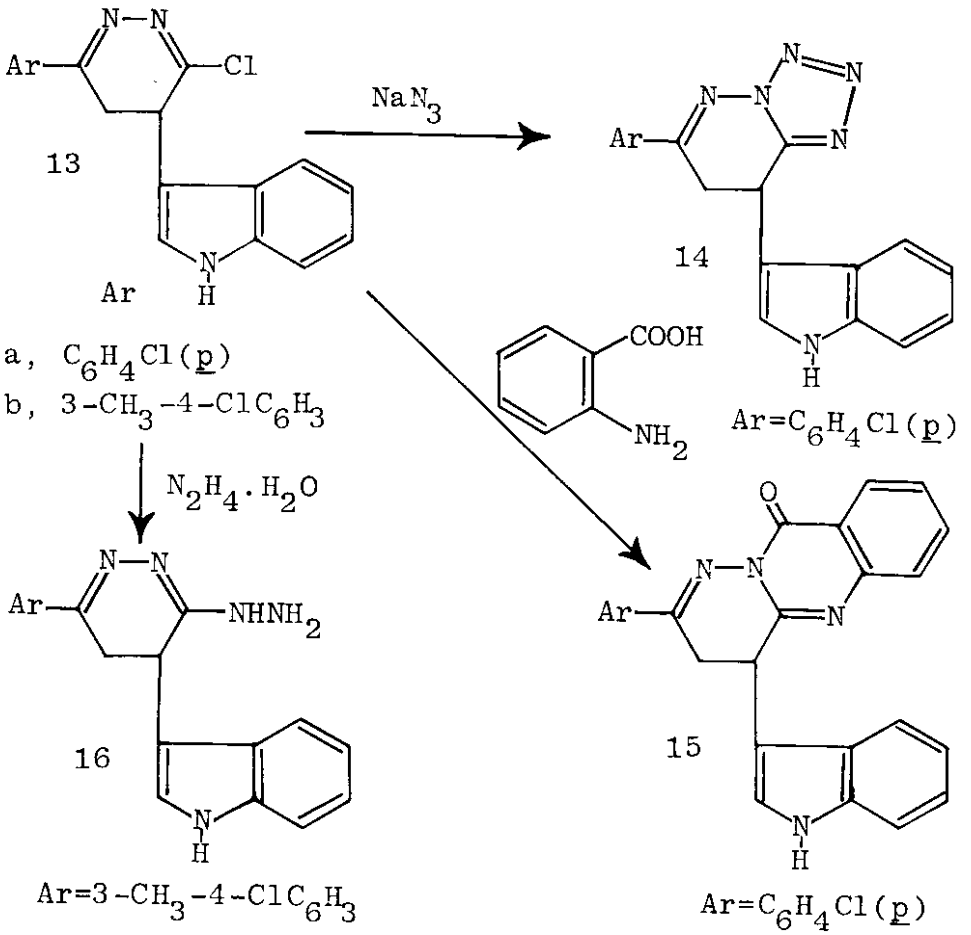
and ν(N-C=S) at 1370 and 1480, respectively. The ^{1}H-n.m.r. spectrum of 20 in $CDCl_3$ exhibited signals at 8.1 - 6.9 (14 H,m,ArH + NH.CH), 4.4 (2 H,s,CH_2), 2.2 (3 H,s,CH_3).

Experimental

The infrared absorption spectra were determined with a Unicam SP 1200 spectrophotometer using KBr Wafer technique. The ^{1}H-n.m.r. spectra were recorded with a Varian VN 1009 (S-60T) instrument, the position of peaks is expressed in ppm (δ-values), TMS as internal standard. The mass spectra were obtained on an AEI MS 902 mass spectrometer at 70 eV electron energy, 6KV accelerating voltage and an ion source temperature of 130° using the direct insertion probe. UV spectra in ethanol were recorded on a Coleman-Hitachi 124 double beam instrument (λ_{max} in nm). All melting points are uncorrected.

Reaction of 1a and 1b with indoles. Formation of 2a-d.

To a solution of 1a or 1b (0.01 mole) in dry benzene (20 ml), was



added inole or 1,2-dimethylindole (0.01 mole) and the reaction mixture refluxed for 10 hours. The solid that separated on cooling was crystallized from a suitable solvent to give 2a-d, respectively.

Condensation of acid 2c with aromatic aldehydes. Formation of 3a and 3b.

A solution of 2c (0.01 mole), p-chlorobenzaldehyde or p-nitrobenzaldehyde (0.01 mole), piperidine (few drops) in ethanol (30 ml) was refluxed for 4 hours. The solid separated after cooling was crystallized from a suitable solvent to give 3a and 3b.

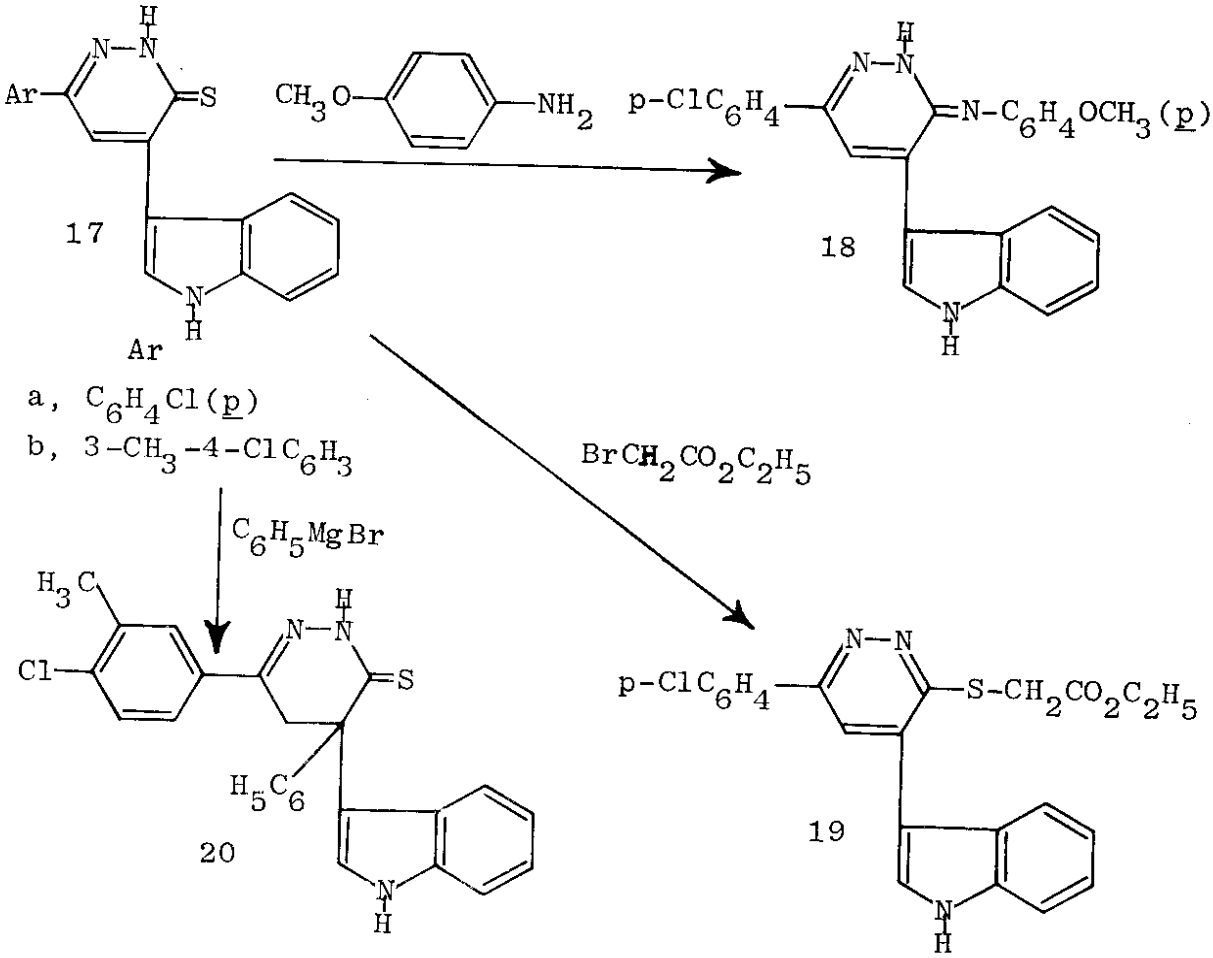
Conversion of acids (2) to butenolides 4.

Method A

A solution of acids (2a or 2c) (0.01 mole) in acetic anhydride (20 ml) was refluxed for 4 hours. The solid obtained after concentration and cooling was crystallized from a suitable solvent to give the butenolides 4a and 4b.

Method B

The acid (2a or 2c) (0.01 mole) was heated at its melting point for 30 minutes and the resulting solid crystallized from a suitable solvent to give the butenolides 4a and 4b.



Hydrolysis of butenolide (4). Formation of acid (2)

A solution of 4a or 4b (1 g) in ethanol (10 ml) was treated with sodium hydroxide (1 g in 5 ml water), then heated under reflux for 2 hours. The cooled solution was acidified with dilute hydrochloric acid and the precipitate was crystallized from a suitable solvent and identified as 2a and 2c by m.p. and mixed m.p. determination.

Condensation of 4b, 2a-d, 13b and 17a with hydrazines and amines. Formation of 5a, 5b, 6a-d, 7a-d, 16 and 18.

A mixture of 4b, 2a-d, 13b or 17a (0.01 mole) and hydrazine hydrate, phenylhydrazine or amines, namely ethanolamine, benzylamine or p-anisidine (0.015 mole) in ethanol or acetic acid (20 ml) was refluxed for 3 hours. The solid that separated after concentration and cooling was crystallized from suitable solvent to give 5a, 5b, 6a-d, 7a-d, 16 and 18, respectively.

Action of dimethylsulfate, diethylsulfate and ethylbromoacetate on dihydropyridazinone 6c and thiopyridazinone 17a

A mixture of 6c or 17a (0.01 mole) anhydrous potassium carbonate (0.03 mole), dimethylsulfate, diethylsulfate or ethylbromoacetate (0.03 mole) and dry acetone (50 ml) was refluxed for 20 hours. After removing the excess solvent the products were crystallized from the proper solvent to give compounds 8a-c and 19, respectively.

Table-1: Physical Data of Various Compounds Prepared

Compd.[+]	M.P. °C	Yield %	Compd.[+]	M.P. °C	Yield %
2a	191	97[(a)]	8b	168	63[(a)]
2b	198	95[(a)]	8c	95	55[(b)]
2c	202	89[(a)]	9	>250	56[(a)]
2d	203	93[(b)]	10[a]	290	48[(c)]
3a	194	58[(a)]	10b	>300	45[(c)]
3b	197	50[(a)]	11	60	42[(d)]
4a	>300	60[(a)]	12	298	50[(a)]
4b	182	67[(a)]	13	270	38[(a)]
5a	166	70[(a)]	14a	190	47[(a)]
5b	152	65[(a)]	14b	165	49[(a)]
6a	232	84[(a)]	15	248	74[(b)]
6b	250	87[(a)]	16	285	69[(a)]
6c	187	81[(b)]	17	215	61[(c)]
6d	240	86[(c)]	18a	265	59[(b)]
7a	183	80[(a)]	18b	215	56[(b)]
7b	255	75[(c)]	19	198	51[(a)]
7c	210	79[(a)]	20	105	48[(d)]
7d	230	88[(c)]	21	165	33[(a)]
8a	172	66[(b)]			

[+]All compounds gave satisfactory elemental analysis.
Compounds were recrystallized from (a) ethanol (b) benzene(c) acetic acid (d) light petroleum (60-80°).

Condensation of anisaldehyde with 6a. Formation of 9.

A warm solution of 6a (0.01 mole) in ethanol (20 ml) was treated with an ethanolic KOH solution (25 ml; 4%) and anisaldehyde (0.01 mole) added portionwise with continuous shaking. The reaction mixture was refluxed for 2 hours, cooled, poured into cold water and the solid obtained crystallized from the proper solvent to give 9.

Synthesis of pyridazinone 10a and 10b

The solution of dihydropyridazinone 6a and 6c (0.01 mole) in glacial acetic acid (20 ml) was sitrred and treated portionwise with bromine at 60-70°. The solution was stirred for a further 2 hours, then cooled in ice. The precipitated product was filtered off, washed with light pet. (40-60°), and stirred with concentrated ammonium hydroxide for 15 minutes. The solid product was crystallized from a suitable solvent to give 10a-b.

Action of Grignard reagents on pyridazinone 10b, dihydropyridazinone 6a and 6c or thiopyridazinone 17b. Formation of 11,12 and 20.

The solution of Grignard reagents namely, phenylmagnesium bromide or p-methoxyphenylmagnesium bromide (prepared from 0.03 mole of alkyl or arylhalide and 0.03 atoms of magnesium) was added to a solution of 10b, 6a, 6c and 17b (0.01 mole) in dry ether. The solution obtained was refluxed for 4 hours in a boiling water bath and left overnight. The reaction mixture was then hydrolysed with saturated solution of ammonium chloride, extracted with ether, and the solvent removed to give a solid product which was crystallized from a suitable solvent to give 11,12 and 20 respectively.

Reaction of 6a and 6c with $POCl_3$. Formation of 13a and 13b.

A mixture of 6a or 6c (0.01 mole) and $POCl_3$ (10 ml) was gently refluxed for 30 minutes, cooled, treated with crushed ice and the precipitated solid filtered and crystallized from a suitable solvent to give 13a and 13b respectively.

Reaction of 13a with sodium azide. Formation of 14.

A mixture of 13a (1 g), sodium azide (1 g), water (5 ml) and dimethylformamide (20 ml) was boiled for 2 hours and cooled. The solid obtained upon dilution with water was filtered and crystallized from a suitable solvent to give 14.

Reaction of 13a with anthranilic acid. Formation of 15

A mixture of 13a (0.01 mole) and anthranilic acid (0.01 mole) was heated in an oil-bath at 150°C for 1 hour, cooled and triturated with ethanol. The solid obtained was crystallized from a suitable solvent to give 15.

Action of P_2S_5 on the dihydropyridazinones 6a and 6c. Formation of 17a and 17b.

A solution of 6a or 6b (0.01 mole) P_2S_5 (0.02 mole) and dry xylene (50 ml) was boiled under reflux for 6 hours. The reaction mixture was filtered while hot and then concentrated. The product which separated on cooling was crystallized from a suitable solvent to give the thione derivative 17a and 17b respectively.

References

1. S.Aurelia, G.Stanislov, J.Julia and H.Anna, *Agrochemia*, **9**, *129 (1969)*,

2. Konecny-Vaclav, *Pesti.Sci.*, **4**, *775(1973)*
3. S.Barlogova, and J.Grunt, *Cesk.Hyg.*, **20**, *5 (1975)*
4. W.V.Curran and A.Ross., *J.Mednl.Chem.*, **17**, *237 (1974)*
5. F.J.McEvoy and C.R.Allen, *J.Mednl.Chem.*, **17**, *284(1974)*
6. R.Jaunin, *Chim.Ther.*, **2**, *317 (1967)*
7. S.Kamiya, A.Nakamira, T.Itai, K.Koshinuma and G.Okusa, *Yakugaku Zasshi*, **86**, *1099 (1966)*
8. Y.S.Rao, *Chem.Rev.*, **64**, *369 (1964)*
9. G.H.Sayed and M.S.Abd-Elhalim, *Indian J.Chem.*, **20B**, *424 (1981)*
10. G.H.Sayed, El-Kady and M.S. Abd-Elhalim, *Indian J.Chem.*, **20B**, *845 (1981)*
11. A.M.Kaddah, and A.M.Khalil, *Indian J.Chem.*, **15B**, *1025 (1977)*
12. A.K.Fateen, S.M.A.R. Omaran, A.M.Kaddah and A.H. Moustafa, *Indian J.Chem.*, **14B**, *276 (1976)*
13. E.Lieber, D.Levering and L. Patterson, *Anal.Chem.*, **23**, *1594 (1951)*
14. A.R.Katritzky, "Physical Methods in Heterocyclic Chemistry" Vol.2 (Academic Press, New York 1963), 270.
15. G.H.Sayed, M.El-Kady and M.A. Elhashash, *Rev.Roumaine Chim.*, **25**, *1375 (1980)*