CCA-356

547.751-8:547.5
Original Scientific Paper

Indole Compounds. IV.* Substituent Effects on the Cyclization of Phenylhydrazines with Acetals into *Bz*,3-Disubstituted Indoles

*D. Desaty*** *and D. Keglević*

Tracer Laboratory, Institute »Ruđer Bošković«, Zagreb, Croatia, Yugoslavia

Received January 8, 1965

The condensation of a number of phenylhydrazine hydrochlorides with various acetals in 25% acetic acid at 50—80° was investigated and several new indoles prepared. It was established that under these conditions the determinant factor for a successful indolization is the presence of a nucleophilic substituent in *para*- or less favourably in *ortho*- position on the aromatic nucleus of the phenylhydrazine moiety. The nature of the aliphatic acetal moiety (unsubstituted, 4-amino, 3- or 4-acylamino, 3-cyano) does not effect substantially the relative ease of indolization. When free aldehydes were used instead of the corresponding aliphatic unsubstituted diethyl acetals, the yields on 5- or 7-substituted-3--alkylindoles dropped considerably. The smooth syntheses of 5-benzyloxy-, 5-methoxy-, and 5-ethoxy-indole-3-acetonitriles suggest this way as a preparative method for these compounds.

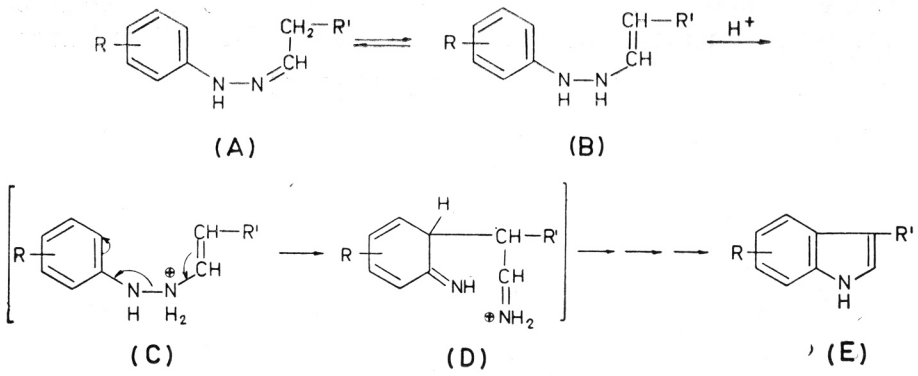
It has been found[1–3] that *p*-benzyloxy- and *p*-methoxy-phenylhydrazine hydrochlorides condense under mild conditions with 4-amino-, *N*,*N*-disubstituted-4-amino-, as well as with 4-acetylamino- butanal diethyl acetals into the corresponding tryptamine derivatives. Since by this modified Fischer indole synthesis a number of biologically interesting 3,5-disubstituted indoles had been prepared in fair to very good yields, it seemed to us of interest to examine the scope and principal limitations of this reaction. The present paper is concerned with the effects of the nature of the reactants on the readiness of the indole formation. The indoles described in this paper are given in Chart I, and the yields of all indoles synthesized so far by this method are tabulated in Table I.

All the reactions were conducted with equimolar amounts of the reactants in 25% acetic acid solution (water or water-ethanol 1:2) at 50—80° for 2.5—5 hours. Firstly, an attempt was made to correlate the relative ease of indolization with the effects of the substituents on the aromatic ring of the phenylhydrazine moiety. Hence, 4-aminobutanal diethyl acetal was subjected to condensation with several phenylhydrazine hydrochlorides. Earlier experiments from this laboratory have already shown[1] that under the reaction conditions mentioned above, phenylhydrazine bearing electrophylic nitro groups would not cyclize with 4-aminobutanal diethyl acetal into the cor-

* Part III.: D. Desaty and D. Keglević, *Croat. Chem. Acta* **36** (1964) 103.

** Part of this paper is taken from the Thesis of D. Desaty, presented to the University of Zagreb, 1964, in partial fulfilment of the requirements for the degree of Doctor of Chemistry (Ph. D.).

responding indole derivative. It is known[4] that the Fischer indole synthesis is facilitated with electron-releasing groups which add to the polarizability of the enhydrazine intermediate (*B*) and thus increase the electron density at C-2 position of the aromatic nucleus (*C*) where the formation of the new *C*—*C* bond (*D*) takes place:



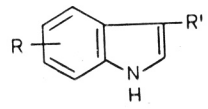
The condensation of unsubstituted phenylhydrazine hydrochloride with 4-aminobutanal diethyl acetal failed; only traces of tryptamine could be detected by paper chromatography. *p*-Ethoxyphenylhydrazine hydrochloride condensed with the same acetal into 5-ethoxytryptamine (I), the yield of the isolated I picrate corresponding well with the yields of 5-methoxy- and 5-benzyloxy-tryptamines prepared already[1] in this manner. The reaction with *m*-benzyloxy-phenylhydrazine hydrochloride failed under these conditions, while *o*-methoxyphenylhydrazine hydrochloride gave 7-methoxytryptamine (II), although in a considerably lower yield than the corresponding *p*-methoxy analogue[1].

The moderate activity of *o*-methoxyphenylhydrazine hydrochloride was further demonstrated with some *N,N*-disubstituted 4-aminoacetals[5]. In all three cases *N,N*-disubstituted 7-methoxyptamines III—V were formed; the yields were again considerably lower from those of the 5-methoxy analogues prepared under the same conditions[3].

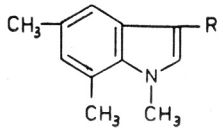
To obtain further evidence, the condensations of *m*-benzyloxyphenylhydrazine hydrochloride with butanal diethyl acetal and 3-phthalimidopropanal diethyl acetal (XXIV) were attempted. However, in the reaction mixtures only negligible amounts of impure indole products could be detected. An effort was then made to prepare 3-phthalimidopropanal *m*-benzyloxyphenylhydrazone (XXVI); XXVI failed to undergo cyclization when treated with 25% acetic acid at 80°. Under identical conditions neither butanal phenylhydrazone[6] could be indolized. It should be pointed out that several attempts to prepare a true hydrazone in acid media from *p*-benzyloxyphenylhydrazine and butanal, 3-phthalimidopropanal (XXV), or their diethyl acetals respectively, were always unsuccessful; in the reaction mixtures only the starting material and the already formed indole compound could be detected.

Finally, the condensation with a polysubstituted phenylhydrazine bearing groups which exhibit a strong $+I$ effect was tried. *N*-(2,4-Dimethylphenyl)-*N*--methylhydrazine hydrochloride[7] gave with butanal diethyl acetal a low yield of IX, while with 3-phthalimidopropanal diethyl acetal a moderate yield of XVIII was obtained.

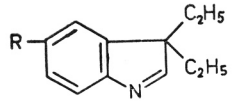
CHART I



	R	R'		R	R'
I	5-OC_2H_5	$CH_2CH_2NH_2$	XIII	5-OCH_2Ph	$CH_2CH_2NHCOPh$
II	7-OCH_3	$CH_2CH_2NH_2$	XIV	5-OCH_2Ph	$CH_2N(CO)_2C_6H_4$
III	7-OCH_3	$CH_2CH_2N(C_2H_5)_2$	XV	5-OCH_3	$CH_2N(CO)_2C_6H_4$
IV	7-OCH_3	$CH_2CH_2N(CH_2)_4$	XVI	5-OC_2H_5	$CH_2N(CO)_2C_6H_4$
V	7-OCH_3	$CH_2CH_2N(CH_2)_5$	XVII	7-OCH_3	$CH_2N(CO)_2C_6H_4$
VI	5-OCH_3	CH_2CH_3	XIX	5-OCH_2Ph	CH_2CN
VII	7-OCH_3	CH_2CH_3	XX	5-OC_2H_5	CH_2CN
VIII	5-OCH_2Ph	$CH_2(CH_2)_6CH_3$	XXI	5-OCH_3	CH_2CN
XII	5-OC_2H_5	$CH_2CH_2NHCOCH_3$	XXII	7-OCH_3	CH_2CN



	R
IX	CH_2CH_3
XVIII	$CH_2N(CO)_2C_6H_4$



	R
X	OCH_2Ph
XI	OCH_3

These results show that for a successful reaction under the described conditions, the phenylhydrazine moiety should bear a nucleophilic substituent either in *para*- or, less favourably, in the *ortho*- position. The inertness of *ortho*- substituted hydrazones to undergo Fischer indolization has been observed several times[4] and ascribed mainly to steric influence[8]. However, with regard to the proposed mechanism of the Fischer indole synthesis it may be expected[9] that a nucleophilic substituent in *meta*- position of arylhydrazone would facilitate the indolization whereas a substituent in *para*- position would retard the reaction. It has been shown[4] that the reverse effect we have obtained with *p*- and *m*- benzyloxyphenylhydrazine does not occur in the indolization of arylhydrazones where more harsh conditions and/or a more effective catalyst were used. However, Pausacker and Schubert[10] found when following kinetically the cyclization of cyclohexanone phenylhydrazones, in glacial acetic acid at 44.7°, that the *p*-methoxy derivative cyclizes immeasurably more rapidly than the *m*-methoxy compound. Hence, it seems that the results we obtained can be rationalized by assuming that under mild conditions employed, the substituent on the aromatic nucleus of the phenylhydrazine moiety should be able to exert an appreciable mesomeric contribution to the formation of the enhydrazine (*B*) as well as to the polarization of the resulting conjugated system (*C*).

Further experiments were done to determine the effect of the acetal moiety on the relative ease of indolization. In order to find out whether a simple unsubstituted aldehyde would undergo indolization in the same yield as the acetal derivative, the condensation of butanal, decanal as well as of their diethyl acetals with *o*- and p- substituted phenylhydrazine hydrochlorides was performed. In all cases with acetals higher yields on 3-alkyl-5- or 7-alkoxyindoles (VII and VIII) were obtained.

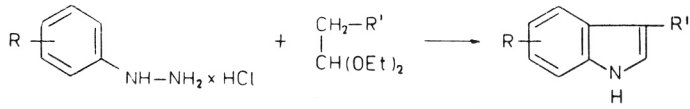
The same effect was produced with 2-ethylbutanal and its diethyl acetal. 3,3,5-Trisubstituted *3H*-indoles (X and XI) were obtained in considerably higher yields when the acetal was used.

Because of our interest on 3-acylaminoalkylindoles substituted in the benzene ring, the reaction of *N*-acylated aminoacetals with phenylhydrazines was studied. *N*-Acetyl-4-aminobutanal diethyl acetal and *p*-ethoxyphenylhydrazine hydrochloride gave a fair yield of the acylated tryptamine XII, an analogue of *N*-acetylserotonin and melatonin, both of which were already prepared[1-2] in this way. *N*-Benzoyl-4-aminobutanal diethyl acetal (XXIII) condensed smoothly with *p*-benzyloxyphenylhydrazine hydrochloride into the acylated tryptamine XIII.

The condensation of 3-phthalimidopropanal diethyl acetal with *p*-substituted phenylhydrazine hydrochlorides resulted in very good yields of easily crystallizable 3-phthalimidomethyl-5-alkoxyindoles XIV—XVI, while again with *o*-methoxyphenylhydrazine hydrochloride a low yield of the 7-methoxy-analogue XVII was obtained. With the same acetal also a moderate yield of the already mentioned trimethyl substituted indole derivative

TABLE I

Yields of Bz,*3-Disubstituted Indoles*
(given in % of theory)



Indole	5-$PhCH_2O$-	5-MeO-	5-EtO-	7-MeO-	1,5,7-tri-Me-
3-(2-aminoethyl)-	**68** [a]	35 [a]	35	8	
3-(2-diethylaminoethyl)-	51 [c]	61 [c]		20	
3-(2-pyrrolidinoethyl)-	65 [c]	76 [c]		18	
3-(2-piperidinoethyl)-	83 [c]	79 [c]		25	
3-ethyl-	53 [a] (20)	49		38 (16)	18
3-octyl-	76 (50)				
3,3-diethyl-*3H*-	54 (37)	25 (15)			
3-(2-acetylaminoethyl)-	68 [b]	26 [a]	41		
3-(2-benzoylaminoethyl)-	70				
3-phthalimidomethyl-	83 (83)	55	48	20 (16)	30
3-cyanomethyl-	61	67	51	11	

Numbers in parenthesis refer to the yields obtained with free aldehydes.
Reported: [a] ref. 1, [b] ref. 2, [c] ref. 3.

XVIII was obtained. The synthesis of XIV and XVII was also performed with 3-phthalimidopropanal which reacted equally well as the acetal XXIV.

The feasibility of this method for the preparation of indol-3-acetonitriles substituted in the benzene ring, prompted us to investigate 3-cyanopropanal diethyl acetal as the aldehydic moiety. Under standard reaction conditions good yields of 5-substituted indole-3-acetonitriles XIX—XXI were obtained. 7-Methoxyindole-3-acetonitrile (XXII) was obtained in an appreciably lower yield.

The described synthesis of 5-substituted indole-3-acetonitriles compares favourably both in yields and in accessibility of precursors with other methods employed for the preparation of these compounds. Moreover, the experimental technique is quicker and simpler than by other procedures. Since the alkaline hydrolysis of the mentioned compounds leads smoothly[11,12] to the corresponding acids, this way seems to be the method of choice for the preparation of 5-hydroxy-, 5-methoxy, and 5-ethoxy-indole-3-acetic acids.

By comparing the yields (Table I) of the prepared indoles, one must take into account that the efficiency of the isolation and purification was not equal for all the products and that it was mainly dependent on the nature of the side-chain at C-3 position. With this in mind it can be concluded that the relative ease of indolization is substantially unaffected by the substituent in the acetal moieties chequed, but that it is strongly dependent upon the position of the nucleophilic substituent in the aromatic ring of the phenylhydrazine moiety.

Summarizing all the results the practical limitation of this reaction appears to be reached in the main with the formation of 3,5-disubstituted indoles bearing at C-5 an electron-releasing group. However, owing to the versatility of the acetal moiety the described indolization proved to be very useful for this class of compounds.

EXPERIMENTAL

All melting points are uncorrected.

Paper chromatography

Descending one-dimensional chromatography was performed on Whatman No. 1 paper in the following solvents: *A* = *n*-butanol — acetic acid — water (60:15:25) and *B* = *iso*propanol — ammonia — water (10:1:1). By spraying with Ehrlich reagent (2% *p*-dimethylaminobenzaldehyde in 5% hydrochloric acid) the tested indoles gave immediately blue spots except the phthalimido derivatives XIV—XVIII where the blue colour appeared after heating the chromatograms to 80° for 20 minutes. *3H*--Indoles X and XI gave green spots after the same treatment and heating. (R_f of picric acid as the reference spot in *A:* 0.72, in *B:* 0.80).

5-Ethoxytryptamine (I) *picrate*

p-Ethoxyphenylhydrazine hydrochloride[13] (0.471 g., 2.5 mmole) was dissolved in 15 ml. of 25% acetic acid at 80° and under stirring the equimolar amount of 4-aminobutanal diethyl acetal[14] (0.401 g.) was dropped in. The stirring and heating was continued for 2.5 hours, whereupon the reaction mixture was cooled, solid potassium carbonate added and I extracted with chloroform. The extracts were dried over anhydrous potassium carbonate, the solvent was evaporated *in vacuo*, and the remaining crude base was dissolved in 20 ml. of ethanol. An equimolar amount of picric acid in hot ethanol was added, and after standing at 0° the red crystals (0.678 g., 63%, m.p. 208°(dec.)) were filtered off, dissolved in acetone and precipitated with water. Yield 0.383 g., 35%, m.p. 218—224° (dec.). For analysis they were recrystallised

from the same solvents, m.p. 225°(dec.), reported[15] 231—233°. R_f in *A:* 0.74, in *B:* 0.70.

Anal. $C_{12}H_{16}N_2O \times C_6H_3N_3O_7$ (419.37) calc'd.: C 49.88; H 4.42; N 16.16%
found : C 49.92; H 4.71; N 16.20%

7-Methoxytryptamine (II) *picrate*

To a stirred solution of *o*-methoxyphenylhydrazine hydrochloride[16] (0.437 g., 2.5 mmole) in 15 ml. of 25% acetic acid kept at 50° 4-aminobutanal diethyl acetal (0.401 g.) was added, and the stirring was continued at this temperature for additional 4 hours. After cooling, solid potassium carbonate was added, and II extracted thoroughly with ether. After the removal of the solvent the remaining oil was chromatographed on an alumina column (20 g.) which was developed with benzene and eluted with acetone. The eluted II was converted to the picrate as described for I. Yield 85 mg. (8%) of red crystals, m.p. 228° (dec.). For analysis it was recrystallised from ethanol, m.p. 230°(dec.), reported[17] 218°. R_f in *A:* 0.72, in *B:* 0.66.

Anal. $C_{11}H_{14}N_2O \times C_6H_3N_3O_7$ (419.35) calc'd.: C 48.69; H 4.09; N 16.70%
found : C 48.95; H 4.15; N 17.01%

N,N-*Disubstituted-7-methoxytryptamines* (III—V)

o-Methoxyphenylhydrazine hydrochloride (2.5 mmole) and the corresponding *N,N*-disubstituted-4-aminobutanal diethyl acetal[5] (2.5 mmole) were condensed in the same way as described for I. After addition of potassium hydroxide the crude base was extracted with ether and purified on alumina as described in general procedure. The Ehrlich positive benzene eluates were pooled and converted to the picrates as described for I.

3-(2-Diethylaminoethyl)-7-methoxyindole (III) *picrate*

Yield: 20%, yellow crystals, m.p. 125—130°. The analytical sample was recrystallised from ethanol, m.p. 141—142°. R_f in *A:* 0.83, in *B:* 0.88.

Anal. $C_{15}H_{22}N_2O \times C_6H_3N_3O_7$ (475.45) calc'd.: C 53.05; H 5.30; N 14.73%
found : C 53.07; H 5.37; N 14.96%

3-(2-Pyrrolidinoethyl)-7-methoxyindole (IV) *picrate*

Yield: 18%, yellow crystals, m.p. 188—190°. The analytical sample was recrystallised from ethanol, m.p. 195—196°. R_f in *A:* 0.82, in *B:* 0.88.

Anal. $C_{15}H_{20}N_2O \times C_6H_3N_3O_7$ (473.43) calc'd.: C 53.27; H 4.90; N 14.79%
found : C 53.47; H 4.79; N 14.89%

3-(2-Piperidinoethyl)-7-methoxyindole (V) *picrate*

Yield: 25%, yellow crystals, m.p. 178—182°. The analytical sample was recrystallised from ethanol, m.p. 182—183.5°. R_f in *A:* 0.84, in *B:* 0.88.

Anal: $C_{16}H_{22}N_2O \times C_6H_3N_3O_7$ (487.46) calc'd.: C 54.20; H 5.17; N 14.37%
found : C 53.88; H 5.51; N 14.65%

In a second identical preparation the benzene eluates were dissolved in hot hexane whereupon the free base crystallised. Pale yellow plates, m.p. 114—115°.

Anal. $C_{16}H_{22}N_2O$ (258.35) calc'd.: C 74.38; H 8.58; N 10.84%
found : C 74.51; H 8.76; N 11.07%

3-(2-Acetylaminoethyl)-5-ethoxyindole (XII)

The condensation of 2.5 mmole *p*-ethoxyphenylhydrazine hydrochloride with equimolar amount of 4-acetylaminobutanal diethyl acetal[1] was carried out in the same manner as described for 5-ethoxytryptamine (I). After cooling, the reaction mixture was extracted with chloroform, the extracts washed with a saturated sodium hydrogen carbonate solution and dried over anhydrous potassium carbonate. After the removal of the solvent the crude oily product was put on an alumina column (21 g.) prepared with benzene — chloroform (1:1) and eluted with the same solvent. Ehrlich positive fractions (No. 3—8, 150 ml.) gave on evaporation a viscous yellow

oil which was dissolved in hot benzene. On cooling, colourless crystals deposited, m.p. 73—77°, yield 41%. For analysis they were twice recrystallised from benzene, m.p. 82—83°. R_f in *A:* 0.90, in *B:* 0.85.

Anal. $C_{14}H_{18}N_2O_2$ (246.30) calc'd.: C 68.27; H 7.37; N 11.38%
found : C 67.91; H 7.12; N 11.46%

The substance was also distilled in a microdistillation tube without decomposition at 0.015 mm., and 200—210° (block temp.).

General procedure for the synthesis of substituted indoles

Compounds VI — XI, XIII — XX and XXII were prepared following the directions given below:

To a stirred solution of the corresponding phenylhydrazine hydrochloride (2.5 mmole) in 50% acetic acid (20 ml.) and ethanol (15 ml.) the equimolar amount of the aldehydic component dissolved in 5 ml. of ethanol was dropped in at 80°. The heating and stirring was continued for 2.5 hours if not stated otherwise.

The reaction mixture was concentrated *in vacuo* to about one third of the volume and the separated oil was extracted with ether. The extracts were washed with saturated sodium hydrogen carbonate solution and dried over potassium carbonate. After the removal of the solvent the crude oily product was treated as described for each particular compound. In few cases the extraction could be omitted because the product crystallised directly from the reaction mixture.

In a number of preparations the crude oily product was purified by alumina column chromatography. Alumina (Lachema, after Brockman) column (25 g., 1×25 cm. for a preparation on 2.5 mmole scale) was prepared with petroleum ether — benzene (1:1), the crude product was dissolved in the same solvent (5 ml.) and put on the column. The column was developed with petroleum ether — benzene (1:1, 50—150 ml.), eluted with benzene (100—200 ml.), the Ehrlich positive benzene fractions pooled and evaporated to dryness.

3-Ethyl-5-methoxyindole (VI) *picrate*

From *p*-methoxyphenylhydrazine hydrochloride and butanal diethyl acetal. The crude oily product was converted to the picrate, yielding 49% of red plates, m.p. 114—116.5°. For analysis they were recrystallised from 50% ethanol, m.p. 116—117°, reported[18] 112°. R_f in *A:* 0.95, in *B:* 0.87.

Anal. $C_{11}H_{13}NO \times C_6H_3N_3O_7$ (404.33) calc'd.: C 50.50; H 3.99; N 13.86%
found: C 50.74; H 4.04; N 14.22%

3-Ethyl-7-methoxyindole (VII) *picrate*

From *o*-methoxyphenylhydrazine hydrochloride and butanal diethyl acetal. The crude oily product was converted to the picrate, yielding 38% of red plates, m.p 134—137°. For analysis they were recrystallised from ethanol, m.p. 136—137°. R_f in *A:* 0.96, in *B:* 0.88.

Anal. $C_{11}H_{13}NO \times C_6H_3N_3O_7$ (404.33) calc'd.: C 50.50; H 3.99; N 13.86%
found : C 50.80; H 4.13; N 14.23%

When butanal was used as the aldehydic component, VII picrate was obtained in 16% yield.

3-Octyl-5-benzyloxyindole (VIII)

From *p*-benzyloxyphenylhydrazine hydrochloride and decanal diethyl acetal. The crude oily product was chromatographed over alumina, and VIII was obtained as a yellow oil in 76% yield. The analytical sample was distilled in a microdistillation tube at 0.01 mm, and 170—180° (block temp.). R_f in *A:* 0.96, in *B:* 0.95.

Anal. $C_{23}H_{29}NO$ (335.47) calc'd.: C 82.34; H 8.71; N 4.18%
found : C 82.34; H 8.84; N 4.40%

When decanal was used as the aldehydic component, VIII was obtained in 50% yield.

3-Ethyl-1,5,7-trimethylindole (IX)

From *N*-(2,4-dimethylphenyl)-*N*-methylhydrazine hydrochloride[7] and butanal diethyl acetal. The crude oily product was dissolved in 15 ml. of hot 50% ethanol and after standing at 0° 18% of IX as colourless plates, m.p. 73—77° were obtained. For analysis they were recrystallised twice from the same solvent, m.p. 81—82° R_f in *A:* 0.94, in *B:* 0.94.

Anal. $C_{13}H_{17}N$ (187.27) calc'd.: C 83.37; H 9.15; N 7.48%
found : C 83.47; H 9.12; N 7.80%

3,3-Diethyl-5-benzyloxy-3H-*indole* (X) *picrate*

From *p*-benzyloxyphenylhydrazine hydrochloride and 2-ethylbutanal diethyl acetal. The crude reddish oil was converted to the picrate yielding 54% of yellow needles, m.p. 126—130°. For analysis they were recrystallised from ethanol, m.p. 134—135°. R_f in *A:* 0.94, in *B:* 0.90.

Anal. $C_{19}H_{21}NO \times C_6H_3N_3O_7$ (508.47) calc'd.: C 59.05; H 4.76; N 11.02%
found : C 59.18; H 5.04; N 11.03%

In a second identical preparation a sample of the reddish oily product was distilled in a microdistillation tube at 0.01 mm. and 146—156° (block temp.), yellow oil. IR-spectrum: 6.1 μ (C=N); no NH stretching absorption at 2.7—3.2 μ.

Anal. $C_{19}H_{21}NO$ (279.27) calc'd.: C 81.68; H 7.58; N 5.01%
found : C 81.56; H 7.62; N 5.04%

When 2-ethylbutanal was used as the aldehydic component, X picrate was obtained in 37% yield.

3,3-Diethyl-5-methoxy-3H-*indole* (XI) *picrate*

From *p*-methoxyphenylhydrazine hydrochloride and 2-ethylbutanal diethyl acetal. The crude oily product was converted to the picrate yielding 25% of yellow crystals, m.p. 111—113°. For analysis they were recrystallised twice from ethanol, m.p. 116—117°. R_f in *A:* 0.96, in *B:* 0.92.

Anal. $C_{13}H_{17}NO \times C_6H_3N_3O_7$ (432.38) calc'd.: C 52.78; H 4.66; N 12.96%
found : C 53.11; H 4.62; N 13.11%

When 2-ethylbutanal was used as the aldehydic component, XI picrate was obtained in 15% yield.

3-(2-Benzoylaminoethyl)-5-benzyloxyindole (XIII)

From *p*-benzyloxyphenylhydrazine hydrochloride and 4-benzoylaminobutanal diethyl acetal (XXIII). From the reaction mixture the crude oily product was extracted with chloroform, the solvent was removed, the residue dissolved in ethyl acetate and XIII precipitated with petroleum ether. Pale brown crystals, 70% yield, m.p. 114—115°, were filtered off and a specimen recrystallised from the same solvents for analysis. Colourless needles, m.p. 117—118°. R_f in *A:* 0.94, in *B:* 0.89.

Anal. $C_{24}H_{22}N_2O_2$ (370.43) calc'd.: C 77.81; H 5.99; N 7.56%
found : C 77.89; H 6.11; N 7.78%

3-Phthalimidomethyl-5-benzyloxyindole (XIV)

From *p*-benzyloxyphenylhydrazine hydrochloride and 3-phthalimidopropanal diethyl acetal (XXIV). The reaction mixture was cooled and left to stand at 0° whereupon XIV precipitated as yellow crystals. Yield: 83%, m.p. 165—170°. For analysis it was recrystallised twice from ethanol. Pale yellow needles, m.p. 173—174°. R_f in *A:* 0.94, in *B:* 0.88.

Anal. $C_{24}H_{18}N_2O_3$ (382.40) calc'd.: C 75.37; H 4.75; N 7.33%
found : C 75.11; H 4.83; N 7.34%

When 3-phthalimidopropanal (XXV) was used as the aldehydic component the yield on XIV was 83%.

3-Phthalimidomethyl-5-methoxyindole (XV)

From *p*-methoxyphenylhydrazine hydrochloride and XXIV. The crude oily product was chromatographed on alumina. The Ehrlich positive benzene fractions gave on evaporation a yellow oil which was dissolved in hot ethanol. On cooling XV precipitated, yield: 55%, m.p. 165—167°. For analysis it was recrystallised from ethanol, pale yellow crystals, m.p. 167—168.5°. R_f in *A:* 0.95, in *B:* 0.87.

Anal. $C_{18}H_{14}N_2O_3$ (306.31) calc'd.: C 70.58; H 4.61; N 9.15%
found : C 70.68; H 4.59; N 9.48%

3-Phthalimidomethyl-5-ethoxyindole (XVI)

Prepared from *p*-ethoxyphenylhydrazine hydrochloride and XXIV in the same way as the 5-methoxy derivative XV. After chromatography over alumina and crystallisation from ethanol, yellow crystals, m.p. 135—137°, yield 48% were obtained. For analysis they were recrystallised from ethanol, m.p. 136—137°. R_f in *A:* 0.95, in *B:* 0.92.

Anal. $C_{19}H_{16}N_2O_3$ (320.33) calc'd.: C 71.24; H 5.03; N 8.75%
found : C 71.56; H 5.11; N 9.03%

3-Phthalimidomethyl-7-methoxyindole (XVII)

Prepared from *o*-methoxyphenylhydrazine hydrochloride and XXIV in the same way as XV. After chromatography and crystallisation from ethanol, yellow needles, m.p. 175—178°, yield 20%, were obtained. For analysis they were recrystallised from ethanol, m.p. 177—179°, pale yellow needles. R_f in *A:* 0.96,, in *B:* 0.91.

Anal. $C_{18}H_{14}N_2O_3$ (306.31) calc'd.: C 70.58; H 4.61; N 9.15%
found : C 70.85; H 4.90; N 9.48%

When 3-phthalimidopropanal (XXV) was used as the aldehydic component, XVII was obtained in a 16% yield.

3-Phthalimidomethyl-1,5,7-trimethyl indole (XVIII)

From *N*-(2,4-dimethylphenyl)-*N*-methylhydrazine hydrochloride and XXIV. The reaction mixture was concentrated *in vacuo* to about one third of the volume and left to stand at 0° overnight. The precipitated XVIII was filtered off; yield: 30%, m.p. 154—157°. For analysis it was recrystallised twice from ethyl acetate, pale yellow needles, m.p. 190—191°. R_f in *A:* 0.97, in *B:* 0.95.

Anal. $C_{20}H_{18}N_2O_2$ (318.36) calc'd.: C 75.45; H 5.70; N 8.80%
found : C 75.79; H 5.69; N 9.02%

5-Benzyloxyindole-3-acetonitrile (XIX)

The condensation was carried out with 2.508 g. (10 mmoles) *p*-benzyloxyphenylhydrazine hydrochloride and 1.572 g. (10 mmoles) 3-cyanopropanal diethyl acetal[19] in 60 ml. of 50% acetic acid and 60 ml. of ethanol as described in general procedure, except that the reaction time was prolonged to three hours. The reaction mixture was worked up, and the crude oily product chromatographed over alumina (65 g.). The column was developed with 75 ml. benzene (discarded) and eluted with the same solvent (150 ml.). On evaporation, benzene eluates left a viscous oil which was dissolved in hot benzene and gradually precipitated with petroleum ether. After standing at 0°, 1.602 g., 61% of yellowish crystals with m.p. 74—76° were obtained. For analysis a sample was recrystallised from benzene — petroleum ether, m.p. 77—78°, reported[11] 75—78°. R_f in *A:* 0.94, in *B:* 0.89.

Anal: $C_{17}H_{14}N_2O$ (262.30) calc'd.: C 77.84; H 5.38; N 10.68%
found : C 77.61; H 5.40; N 10.54%

5-Ethoxyindole-3-acetonitrile (XX)

From *p*-ethoxyphenylhydrazine hydrochloride and 3-cyanopropanal diethyl acetal as described in general procedure except that the condensation time was prolonged to three hours. The crude oily product solidified on standing; it was dissolved in 2 ml. of hot benzene and precipitated with 2 ml. of petroleum ether. After standing at 0° 0.255 g., 51% of brownish crystals, m.p. 92—98° deposited. For analysis they were recrystallised twice from benzene; yellowish crystals, m.p. 101—102°, reported[20] 103—104°. R_f in *A:* 0.93, in *B:* 0.87.

Anal. $C_{12}H_{12}N_2O$ (200.23) calc'd.: N 13.99%
found : N 14.27%

5-Methoxyindole-3-acetonitrile (XXI)

To 0.873 g. (5 mmole) *p*-methoxyphenylhydrazine hydrochloride in 30 ml. of 25% acetic acid, 0.786 g. (5 mmole) of 3-cyanopropanal diethyl acetal was added under stirring at 80°. The stirring and heating was continued for 6 hours, the reaction mixture cooled, solid potassium carbonate added and XXI extracted with ether. The crude oily product was chromatographed over alumina (30 g.) as described in general procedure. Ehrlich positive benzene fractions (No 5—8, 100 ml.) were pooled, evaporated *in vacuo* and chromatographed over a second alumina column (26 g.) prepared with carbon tetrachloride. The column was developed with the same solvent (50 ml.) and eluted with carbon tetrachloride — chloroform (9:1, 200 ml.). The eluates left 0.625 g. (67%) of an oil which gave in solvents *A* and *B* only one Ehrlich positive spot. The compound was reported as a yellow oil without the analytical data[12]. For analysis it was distilled in a microdistillation tube at 0.01 mm. and 160—180° (block temp.), yellowish oil. R_f in *A:* 0.91, in *B:* 0.85.

Anal. $C_{11}H_{10}N_2O$ (186.21) calc'd.: C 70.95; H 5.41; N 15.05%
found : C 70.76; H 5.42; N 15.16%

7-Methoxyindole-3-acetonitrile (XXII)

The reaction was carried out with *o*-methoxyphenylhydrazine hydrochloride and 3-cyanopropanal diethyl acetal following the general procedure, except that the reaction time was prolonged to six hours. The crude oily product was chromatographed over an alumina column which was developed with carbon tetrachloride (50 ml.) and eluted with carbon tetrachloride — chloroform (9:1, 100 ml.). Ehrlich positive fractions (No. 3—5, 75 ml.) were pooled, the solvent evaporated *in vacuo* and the remaining oil dissolved in hot benzene. On cooling 52 mg., 11% of colourless plates deposited, m.p. 146—148°. For analysis they were recrystallised from the same solvent, m.p. 149—151°. R_f in *A:* 0.91, in *B:* 0.87.

Anal. $C_{11}H_{10}N_2O$ (186.21) calc'd.: C 70.95; H 5.41; N 15.05%
found : C 70.71; H 5.46; N 15.22%

4-Benzoylaminobutanal diethyl acetal (XXIII)

4-Aminobutanal diethyl acetal (2.0 g., 12.4 mmole) was dissolved with 0.6 g. (15 mmole) sodium hydroxide in 18 ml. water. Benzoyl chloride (1.83 g., 13 mmole) was dropped in under cooling and the suspension was shaken for additional 30 minutes at room temperature. The mixture was extracted with ether, and the obtained oil distilled at 160—170°/0.01 mm. Yield: 2.05 g., 63%, viscous colourless oil. Reported[21] 187—189°/1 mm.

Anal. $C_{15}H_{23}NO_3$ (265.34) calc'd.: C 67.89; H 8.74; N 5.28%
found : C 67.85; H 8.58; N 5.50%

3-Phthalimidopropanal diethyl acetal (XXIV)

3-Bromopropanal diethyl acetal (9.7 g., 46 mmole, prepared in the same way as the 3-chloro- derivative[22]) was dissolved in 150 ml. of dimethylformamide and to the solution 10 g. (54 mmole) of potassium phthalimide was added. The mixture was stirred at 80—90° for 50 hours, the unreacted potassium phthalimide was filtered off and the filtrate concentrated *in vacuo* to about 30 ml. Water (120 ml.) was added and the oil which separated extracted with chloroform. The extracts were

washed with water, dried (sodium sulphate), the solvent removed *in vacuo* and the obtained oil was distilled at 130—135°/0.015 mm. Yield: 5.2 g., 41%. For analysis a sample was redistilled in a microdistillation tube at 0.01 mm. and 125—130° (block temp.).

Anal. $C_{15}H_{19}NO_4$ (277.31) calc'd.: C 64.96; H 6.91; N 5.05%
found : C 64.97; H 6.94; N 5.27%

3-Phthalimidopropanal (XXV)

The acetal XXIV (3.0 g.) was suspended in 60 ml. of 3% hydrochloric acid and refluxed for 30 minutes. The hot solution was filtered through a layer of carbon and after cooling 1.69 g., 77% of XXV crystallised as white needles, m.p. 115—119°. One recrystallisation from water afforded analytically pure product, m.p. 118—120°. Reported 119—120° [23], 118.5—119° [24].

Anal. $C_{11}H_9NO_3$ (203.19) calc'd.: C 65.02; H 4.47; N 6.89%
found : C 65.26; H 4.61; N 7.08%

3-Phthalimidopropanal m-*benzyloxyphenylhydrazone* (XXVI)

A solution of 3-phthalimidopropanal (XXV, 0.203 g., 1 mmole) and *m*-benzyloxyphenylhydrazine base[1] (0.214 g., 1 mmole) in absolute benzene (20 ml.) was refluxed under exclusion of moisture for 8 hours. The solvent was removed *in vacuo*, and the solid residue crystallised from ethanol. Yield: 0.30 g. (75%) of yellow crystals, m.p. 106—113°. For analysis they were recrystallised from ethanol, m.p. 112—114°.

Anal.: $C_{24}H_{21}N_3O_3$ (399.43) calc'd.: C 72.20; H 5.29; N 10.52%
found : C 72.23; H 5.04; N 10.81%

Acknowledgment. The authors are indebted to Mrs. Đ. Orlić for the technical assistance, and to Mrs. O. Hadžija B. Sc. and Miss N. Horvatić for the microanalyses.

REFERENCES

1. D. Keglević, N. Stojanac, and D. Desaty, *Croat. Chem. Acta* **33** (1961) 83.
2. D. Desaty, O. Hadžija, S. Iskrić, D. Keglević, and S. Kveder, *Biochim. Biophys. Acta* **62** (1962) 179.
3. D. Desaty and D. Keglević, *Croat. Chem. Acta* **36** (1964) 103.
4. B. Robinson, *Chem. Rev.* **63** (1963) 373.
5. D. Keglević and B. Leonhard, *Croat. Chem. Acta* **35** (1963) 175.
6. J. v. Braun and O. Bayer, *Ber.* **58** (1925) 387.
7. H. H. Stroh and E. Ropte, *Chem. Ber.* **93** (1960) 1148.
8. C. E. Dalgliesh and F. G. Mann, *J. Chem. Soc.* **1947** 653.
9. R. B. Carlin and E. E. Fischer, *J. Am. Chem. Soc.* **70** (1948) 3421.
10. K. H. Pausacker and C. I. Schubert, *J. Chem. Soc.* **1950**, 1814.
11. A. Stoll, F. Troxler, J. Peyer, and A. Hofmann, *Helv. Chim. Acta* **38** (1955) 1452.
12. J. Szmuszkovicz, W. C. Anthony, and R. V. Heinzelman, *J. Org. Chem.* **25** (1960) 857.
13. J. Altschul, *Ber.* **25** (1892) 1842.
14. R. Lukeš and J. Trojanek, *Chem. listy* **46** (1952) 383.
15. E. Adlerová, I. Ernest, V. Hněvsová, J. O. Jílek, L. Novák, J. Pomykáček, M. Rajšner, J. Sova Z. J. Vejdělek, and M. Protiva, *Collection Czechoslov. Chem. Commun.* **25** (1960) 784.
16. H. Reisenegger, *Ann.* **221** (1883) 314.
17. E. Späth and E. Lederer, *Ber.* **63** (1930) 2102.
18. R. Goutarel, M. M. Janot, A. Le Hir, H. Corrodi, and V. Prelog, *Helv. Chim. Acta* **37** (1954) 1805.
19. A. Wohl, *Ber.* **39** (1906) 1952.
20. T. Hoshino and Y. Kotake, *Ann.* **516** (1935) 76; C. A. **29** (1935) 2956.
21. S. Sugasawa, *J. Pharm. Soc. Japan* **1927** 148; *Beil.* **9** II 171.
22. *Organic Syntheses*, Coll. Vol. 2, John Wiley and Sons, Inc, New York, 1955, p. 137.
23. O. A. Moe and D. T. Warner, *J. Am. Chem. Soc.* **71** (1949) 1251.
24. I. Jambrešić and D. Sunko, *Arhiv. kem.* **23** (1951) 195.

IZVOD

Efekti supstituenata na ciklizaciju fenilhidrazina i acetala u *Bz*,3-disupstituirane indole

D. Desaty i D. Keglević

Ispitivana je mogućnost ciklizacije većeg broja fenilhidrazina s različitim acetalima u 25% octenoj kiselini kod 50—80°. Ustanovljeno je da je uvjet za uspješnu indolizaciju kod tih blagih uvjeta, prisutnost nukleofilnog supstituenta na *para*-, odnosno manje povoljno, na *orto*-položaju fenilhidrazina. Za razliku od fenilhidrazinskog dijela, utjecaj alifatske acetalne komponente (nesupstituirani, 4-amino, 3- ili 4-acilamino, 3-cijano) nije se pokazao u toj mjeri bitan za uspjeh ciklizacije. S obzirom na dobra iskorištenja i pogodne ishodne produkte opisana kondenzacija pokazala se kao vrlo pogodna za sintezu mnogih 3,5-disupstituiranih indola.

TRACER LABORATORIJ
INSTITUT »RUĐER BOŠKOVIĆ«
ZAGREB

Primljeno 8. siječnja 1965.