[Chem. Pharm. Bull. 15(1) 8 ~ 15 (1967)]

UDC 547.754.07

2. Fumio Yoneda, Takayuki Miyamae, and Yoshihiro Nitta : The Syntheses of Some Aminomethylindoles

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By treating with secondary amines chloraceto-*o*-toluidide was converted to aminoaceto-*o*-toluidides, which were cyclized on heating with sodium amide to give 2-aminomethylindoles. N-Benzyl-N-(N,N-dimethylaminoaceto)-*o*-toluidide on treatment with sodium amide was converted to 1-benzyl-2-N,N-dimethylaminomethylindole. N-Benzyl-(or N-*p*-chlorobenzyl-)N-phenylhydrazine was treated with aminoacetones in the presence of a trace of acetic acid to convert the corresponding aminoacetone N-benzyl-(or N-*p*-chlorobenzyl-)N-phenylhydrazones. The indole cyclization of the latter gave 1-benzyl-2-methyl-3-aminoindoles. On treatment of aminoacetones with phenylhydrazine derivatives in ethyl alcohol, methylglyoxal diphenylhydrazone derivatives were obtained.

(Received February 10, 1966)

As part of a research program directed to the investigation of compounds possessing antihistaminic properties, we have recently described the synthesis of some 1,2,3,4-tetrahydroquinolines (II).[1] In these the nitrogen atom of 1-*p*-chlorobenzyl-2-pyrrolidinomethylbenzimidazole (Allercur) (I) was replaced by an ethylene bridge. These compounds showed negligible activity in tests for antihistaminic and antiserotonic activity. However, it was found that some of them possessed mild diuretic and imipramine-like central stimulative activity. The structural resemblance between I and II, in contrast with their remarkable pharmacological difference, stimulated speculation on the basis for the changes in activity. It may be pointed out that the benzimidazole moiety of Allercur (I) is planar and the nitrogen atom of I allows full conjugation of the benzimidazole nucleus; but the ring structure of II is twisted by the ethylene bridge which acts as a barrier to inhibit conjugation. To ascertain the importance of this factor, and with the aim of discovering new agents which show antihistaminic properties comparable to those of I, we have investigated the syntheses of indole derivatives (III) which are isosteric and isoelectronic with I. In the present paper we report the results of some of our investigations.

o-Toluidine reacted with chloracetyl chloride to give chloraceto-*o*-toluidide which on treatment with dimethylamine, diethylamine, pyrrolidine, piperidine and morpholine gave N,N-dimethylaminoaceto-(IV),[2] N,N-diethylaminoaceto-(V), pyrrolidinoaceto-(VI),

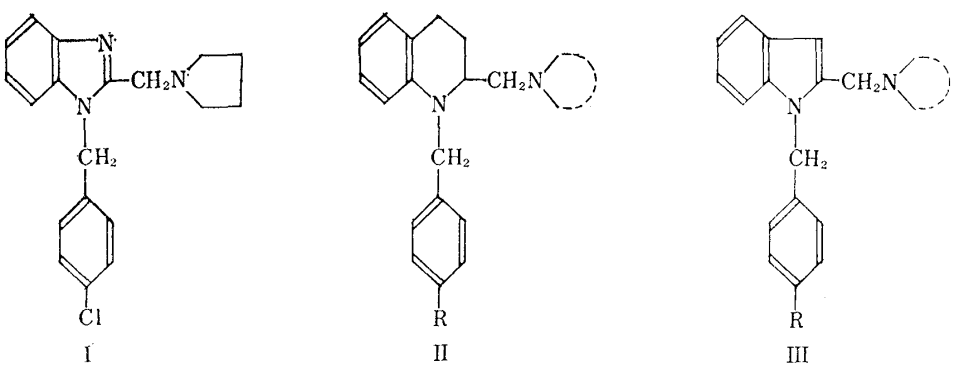

Chart 1.

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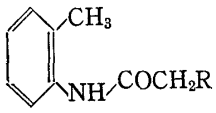
1) F. Yoneda, T. Miyamae, Y. Nitta : This Bulletin, **13**, 500 (1965).

2) H. V. Euler, H. Erdtman : Ann., **520**, 1 (1935).

TABLE I.



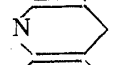
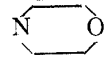
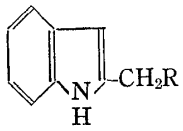
Compd. No.	R	m.p. (°C) picrate	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
IV	$N(CH_3)_2$	166[a]	—	—	—	—	—	—	—
V	$N(C_2H_5)_2$	159	$C_{19}H_{23}O_8N_5$	50.78	5.16	15.58	51.01	5.23	15.75
VI		151	$C_{19}H_{21}O_8N_5$	51.00	4.73	15.65	51.32	4.94	16.01
VII		98[b]	$C_{14}H_{20}ON_2$	72.38	8.68	—	72.33	8.64	—
VIII		77[b]	$C_{13}H_{18}O_2N_2$	66.65	7.74	11.95	66.53	7.81	11.88

TABLE II.



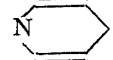
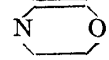
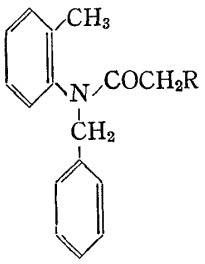
Compd. No.	R	m.p. (°C) picrate	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
IX	$N(CH_3)_2$	183	—	—	—	—	—	—	—
X	$N(C_2H_5)_2$	198	$C_{19}H_{21}O_7N_5$	52.90	4.91	16.24	53.16	4.79	16.32
XI		195	$C_{19}H_{19}O_7N_5$	53.13	4.46	16.31	53.34	4.61	16.29
XII		176	$C_{20}H_{21}O_7N_5$	54.17	4.77	15.80	54.44	4.73	15.78
XIII		190	$C_{19}H_{19}O_8N_5$	51.23	4.30	15.73	51.20	4.33	15.87

TABLE III.



Compd. No.	R	m.p. (°C) picrate	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
XV	$N(CH_3)_2$	145	$C_{24}H_{25}O_8N_5$	56.35	4.93	13.69	56.47	4.99	13.52
XVI	$N(C_2H_5)_2$	154	$C_{26}H_{29}O_8N_5$	57.88	5.42	12.98	58.03	5.43	12.82
XVII		149	$C_{26}H_{27}O_8N_5$	58.09	5.06	13.03	58.14	5.12	12.87
XVIII		103[b]	$C_{21}H_{26}ON_2$	78.22	8.13	8.69	78.30	8.11	8.81
XIX		119[b]	$C_{20}H_{24}ON_2$	77.88	7.84	9.08	77.95	7.76	9.16

a) The free base melts at 58°. *b*) Free base.

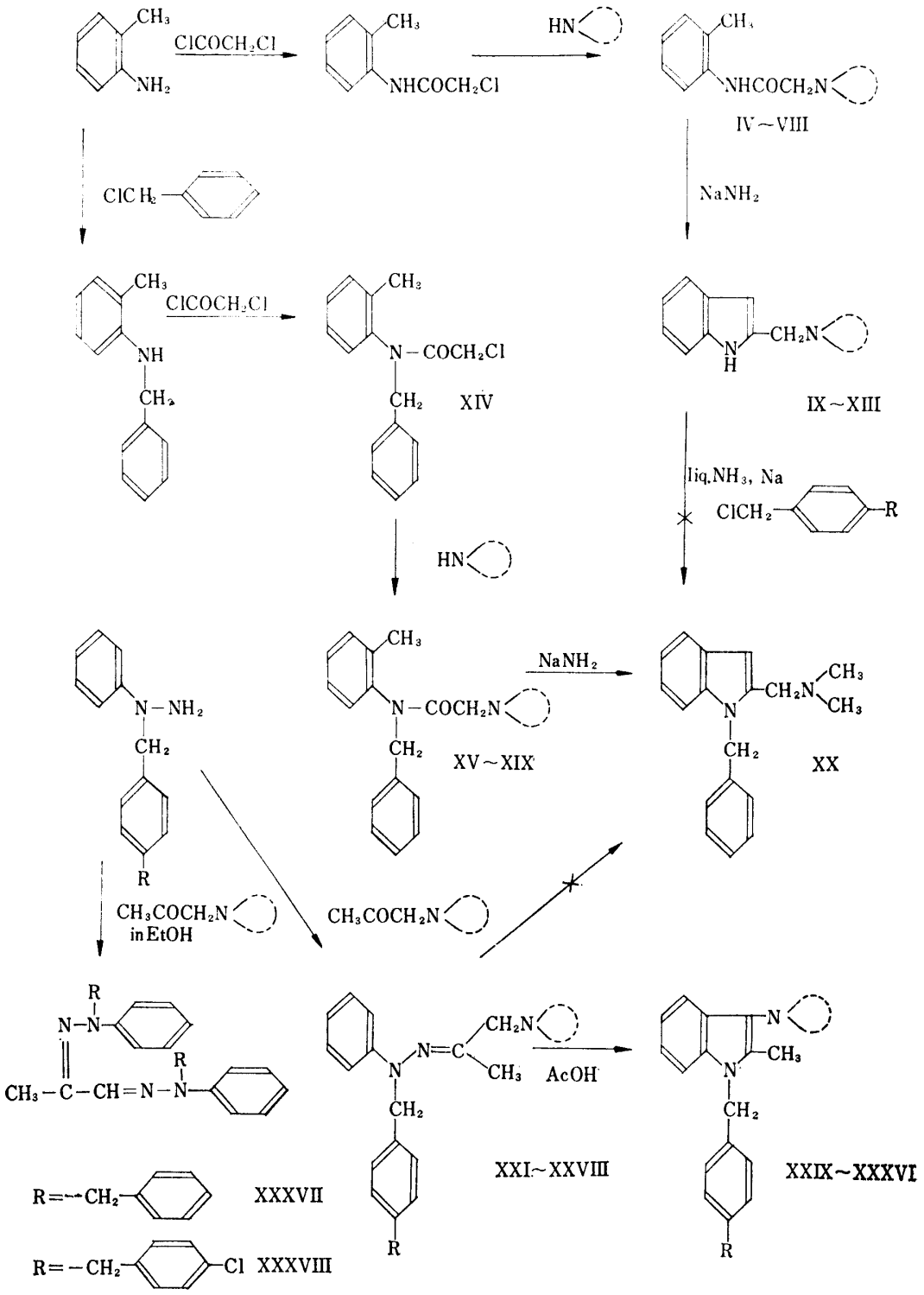
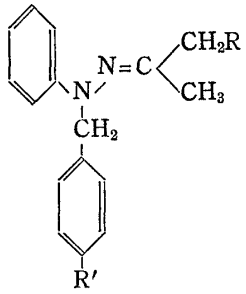


Chart 2.

piperidinoaceto- (Ⅶ), and morpholinoaceto-*o*-toluidide- (Ⅷ) (Table I), respectively. Ⅳ～Ⅷ were cyclized on heating with sodium amide to give 2-N,N-dimethylaminomethyl- (Ⅸ),[3] 2-N,N-diethylaminoethyl- (Ⅹ), 2-pyrrolidinomethyl- (Ⅺ), 2-piperidinomethyl- (Ⅻ) and 2-morpholinomethylindole- (XIII)(Table Ⅱ). The latter on treatment with benzylchloride and *p*-chlorobenzylchloride in liquid ammonia in the presence of sodium amide gave not Ⅲ but unchanged starting material.

3) E. C. Kornfeld : J. Org. Chem., **16**, 806 (1951).

TABLE IV.



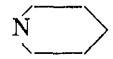
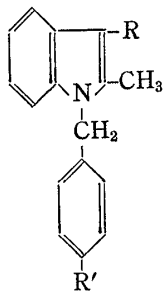
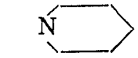
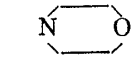
Compd. No.	R	R′	m.p. (°C) picrate	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
XXI	$N(CH_3)_2$	H	95	$C_{24}H_{26}O_7N_6$	56.46	5.13	16.46	56.38	5.17	16.50
XXII	〃	Cl	104	$C_{24}H_{25}O_7N_6Cl$	52.90	4.62	15.42	52.95	4.79	15.39
XXIII	$N(C_2H_5)_2$	H	126	$C_{26}H_{30}O_7N_6$	57.98	5.62	15.61	57.88	5.67	15.99
XXIV	〃	Cl	128	$C_{26}H_{29}O_7N_6Cl$	54.50	5.10	14.67	54.80	5.38	14.64
XXV		H	147	$C_{27}H_{30}O_7N_6$	58.90	5.49	15.27	59.28	5.54	15.27
XXVI	〃	Cl	163	$C_{27}H_{29}O_7N_6Cl$	55.43	5.00	14.27	55.68	5.16	14.43
XXVII		H	134	$C_{26}H_{28}O_8N_6$	56.51	5.11	15.21	56.80	5.13	15.38
XXVIII	〃	Cl	144	$C_{26}H_{27}O_8N_6Cl$	53.20	4.64	14.32	53.24	4.70	14.37

TABLE V.



Compd. No.	R	R′	m.p. (°C) picrate	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
XXIX	$N(CH_3)_2$	H	86	$C_{18}H_{20}N_2$	81.78	7.63	—	82.07	7.38	—
XXX	〃	Cl	97	$C_{18}H_{19}N_2Cl$	72.35	6.41	9.37	72.42	6.31	9.48
XXXI	$N(C_2H_5)_2$	H	74	$C_{20}H_{24}N_2$	82.14	8.27	—	82.35	8.02	—
XXXII	〃	Cl	69	$C_{20}H_{23}N_2Cl$	73.49	7.09	—	73.21	7.39	—
XXXIII		H	112	$C_{21}H_{24}N_2$	82.85	7.95	9.20	82.89	7.84	9.30
XXXIV	〃	Cl	76	$C_{21}H_{23}N_2Cl$	74.43	6.84	8.27	74.54	6.84	8.05
XXXV		H	94	$C_{20}H_{22}ON_2$	78.40	7.24	9.14	78.22	7.14	8.99
XXXVI	〃	Cl	109	$C_{20}H_{21}ON_2Cl$	70.47	6.21	8.22	70.42	6.03	8.46

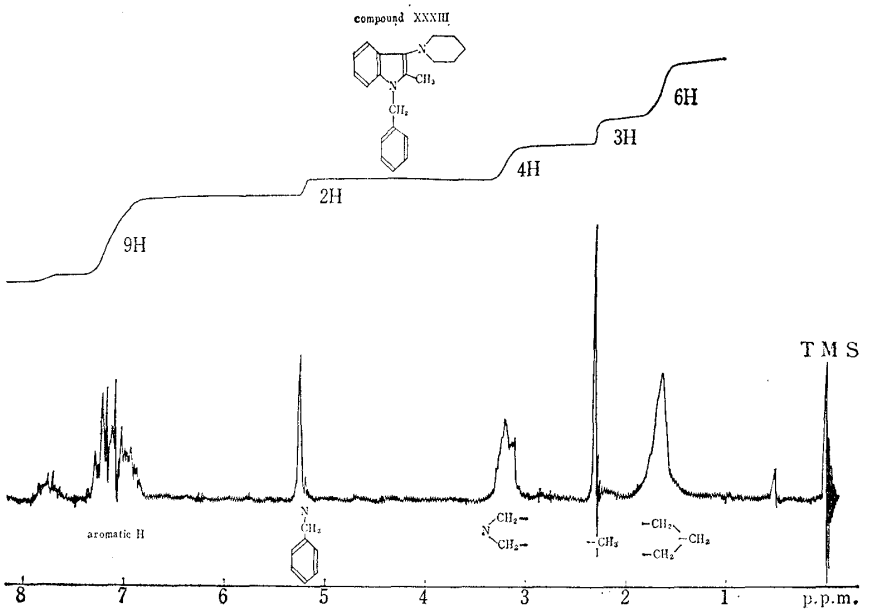


Fig. 1.

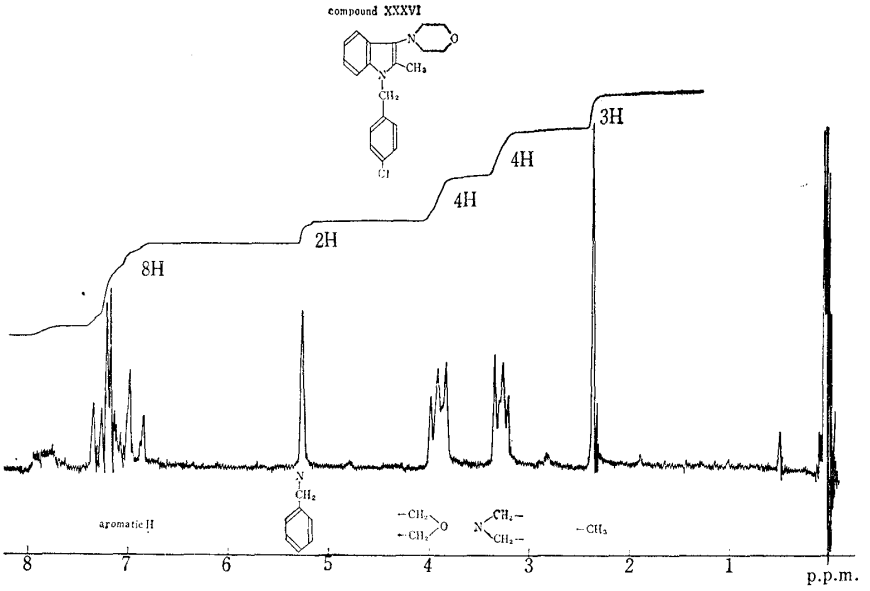
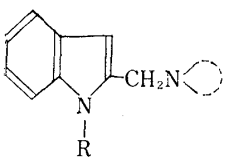


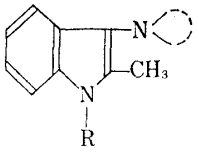
Fig. 2.

To obtain Ⅲ, therefore, *o*-toluidine was beforehand converted to N-benzyl-*o*-toluidine, which on treatment with chloracetyl chloride gave N-benzyl-N-chloraceto-*o*-toluidine (XIV). Treatment of the latter with dimethylamine, diethylamine, pyrrolidine, piperidine and morpholine yielded the corresponding N-benzyl-N-aminoaceto-*o*-toluidides (XV～XIX) (Table Ⅲ). XV～XIX on treatment with sodium amide were converted to Ⅲ, and underwent thermal decomposition to give 1-benzyl-2-N,N-dimethylaminomethylindole (XX) in poor yield as the only isolable product.

As an alternative procedure for the preparation of the compound type corresponding to structure Ⅲ, the application of Fischer's indole synthesis was attempted. N-Benzyl-(or N-*p*-chlorobenzyl-)N-phenylhydrazine was treated with N,N-dimethylamino-, N,N-diethylamino-, piperidino- and morpholino-acetone in the presence of a trace of acetic acid to convert the corresponding aminoacetone N-benzyl-N-phenylhydrazones (XXI～XXVⅢ) at room temperature (Table Ⅳ). Here it might be supposed that cyclization of the latter with acetic acid would give one of the two isomers of



type A



type B

Chart 3.

type A or B. On heating of XXI～XXVIII in the presence of a trace of anhydrous acetic acid, indole cyclization occurred to give 1-benzyl-2-methyl-3-aminoindoles (XXIX～XXXVI) (type B) (Table V) without giving type A and the structures of compounds XXIX～XXXVI were assigned on the basis of the following facts. These compounds were crystalline and did not form picrates, whereas XX (type A) prepared above was an oily substance giving a picrate. Moreover, they (type B) possessed the characteristic absorption of indole derivatives in the ultraviolet spectra at the wavelength of 286 and 293 mμ in ethanol, and a sharp singlet band of three methyl protons at τ7.7 in the nuclear magnetic resonance (NMR) spectra in deuteriochloroform. The NMR spectrum of XXXIII, *e.g.*, exhibited bands at τ8.5 (6H, $-CH_2-$), 7.7 (3H, $-CH_3$), 6.8 (4H, $-CH_2N$), 4.8 (2H, N-aralkyl protons) and 2.9 (9H, aromatic protons).

By heating aminoacetones with N-benzyl-(or N-*p*-chlorobenzyl-)N-phenylhydrazine in the presence of a trace of anhydrous acetic acid without isolation of the corresponding hydrazones (XXI～XXVIII), 1-benzyl-2-methyl-3-aminoindoles (XXIX～XXXVI) were obtained as the major products. Small amounts of the unexpected byproducts, XXXVII (m.p. 126°, in the case of N-benzyl-N-phenylhydrazine) and XXXVIII (m.p. 175°, in the case of N-*p*-chlorobenzyl-N-phenylhydrazine) were also formed. When the above reaction was attempted in solvents such as ethyl or methyl alcohol in the presence or absence of a trace of anhydrous acetic acid, no indole derivatives but only XXXVII or XXXVIII was obtained in moderate yield. The infrared and ultraviolet spectra of these compounds did not show the characteristic absorptions of indole derivatives and it was noteworthy that this reaction gave the identical product (XXXVII or XXXVIII) in spite of the difference of the amine substituent of the aminoacetone. XXXVII and XXXVIII were concluded to be methylglyoxal di-N-benzyl-N-phenylhydrazone and methylglyoxal di-N-*p*-chlorobenzyl-N-phenylhydrazone from the respective molecular formulas, $C_{29}H_{28}N_4$ and $C_{29}H_{26}N_4Cl_2$, and the NMR spectrum of XXXVII [τ8(s, $-CH_3$), 6.1(s,$-CH_2-$),

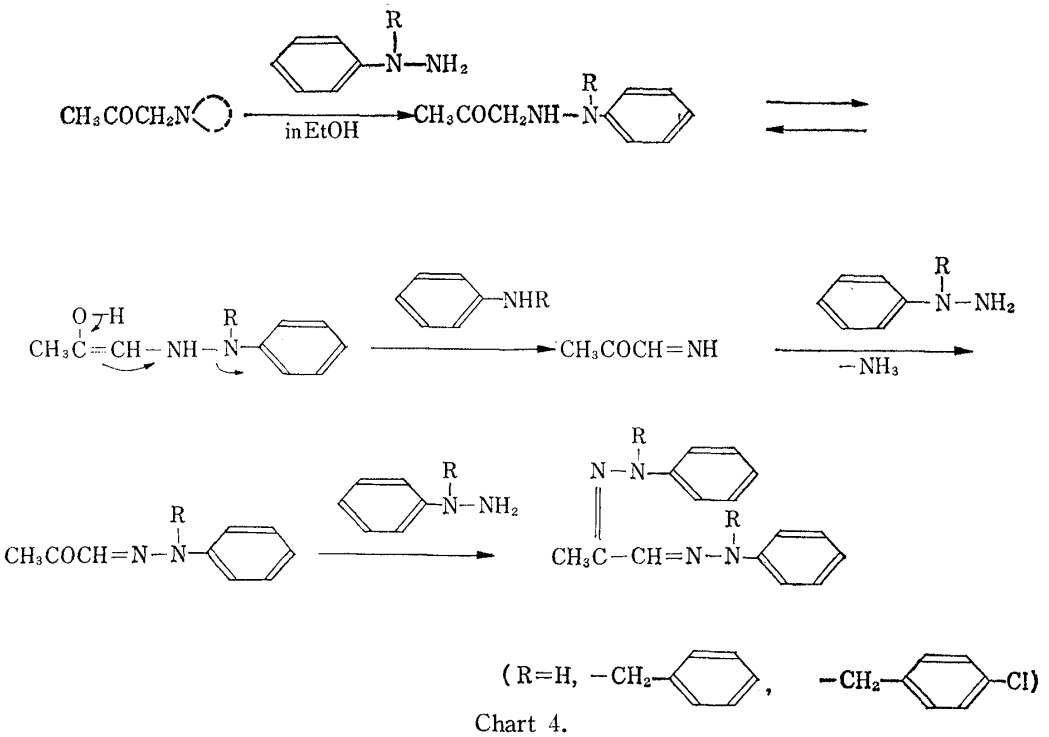


Chart 4.

5.8 (s, $-CH_2-$)]. Therefore the latter were synthesized from methylglyoxal and N-benzyl-(or N-*p*-chlorobenzyl-)N-phenylhydrazine, and proved to be identical with XXXVII and XXXVIII by mixture melting points and by comparison of their infrared spectra. On treatment of aminoacetones with an excess of phenylhydrazine in ethyl alcohol in order to examine the generality of this reaction methylglyoxal diphenylhydrazone was obtained as expected. These observations are relevant to the recent report by Hauptman, *et al.* that the reaction of phenacylbromide with hydrazine in ethyl alcohol results in the formation of phenylglyoxal monohydrazone.[4] The formation of methylglyoxal diphenylhydrazones described above is rationalized in the analogous reaction mechanism of Hauptman as seen in Chart 4.

Experimental*2

N,N-Dimethylaminoaceto-*o*-toluidide (IV)[2]——A mixture of chloroaceto-*o*-toluidide (18.4 g., 0.1 mole) and 10 g. (0.22 mole) of dimethyl amine in 100 ml. of MeOH was maintained in a pressure bottle at 60～70° for 3 hrs. The cooled reaction mixture was evaporated to remove the MeOH, the residue was added to 50 ml. of H_2O, and made strongly basic with 40% aqueous NaOH. The separated oil was extracted with ether; and the extract was dried, concentrated, and distilled to give 14 g. of product, b.p. 135～138° (4 mm.). The picrate melted at 165～166° (from MeOH).

The other compounds of Table I and Table III were similarly prepared.

2-N,N-Dimethylaminomethylindole (IX)[3]——Sodium (4.6 g., 0.2 mole) was converted to sodium amide in 180 ml. of liquid ammonia using a trace of ferric chloride as catalyst. Then N,N-dimethylaminoaceto-*o*-toluidide (16g ., 0.08 mole) was added, and while stirring the excess ammonia was evaporated by passing a stream of dry nitrogen over the mixture. The flask was then immersed in a Wood's metal bath at 150°, and the bath was heated to 310°, during 22 min. The reaction mixture was cooled under nitrogen, and 50 ml. of EtOH added cautiously, followed by 150 ml. of H_2O. The mixture was distilled to remove a little *o*-toluidine, and the residue was cooled and extracted with 80 ml. of ether. The extract was washed with H_2O, and then extracted with dilute aqueous HCl, made alkaline with an excess of Na_2CO_3, the separated oil extracted with ether, and the ether solution dried, and fractionated to give 9.3 g. 2-N,N-dimethylaminomethylindole, b.p. 143～145° (6 mm.). The picrate was prepared and crystallized from EtOH. M.p. 182～184°.

The other compounds of Table II were similarly prepared.

1-Benzyl-2-N,N-dimethylaminomethylindole (XX)——By employing the above procedures, XX was prepared from N-benzyl-N-(N,N-dimethylaminoaceto)-*o*-toluidide. The m.p. of the picrate remained constant of m.p. 212°, after recrystallization from EtOH. *Anal.* Calcd. for $C_{24}H_{23}O_7N_5$: C, 58.42; H, 4.70; N, 14.19. Found: C, 58.61; H, 4.72; N, 14.32.

N-Benzyl-N-chloraceto-*o*-toluidide (XIV)——A solution of N-benzyl-*o*-toluidine (18.3 g., 0.1 mole) in dry benzene (50 ml.) was cooled in an ice bath. A solution of chloracetyl chloride (11.3 g., 0.1 mole) in dry benzene (20 ml.) was then added dropwise with stirring over period of 1 hr. with continued cooling. The mixture was stirred for an additional 5 min. and then poured onto crushed ice. The organic layer was separated, dried and concentrated under reduced pressure. The residue was distilled and the fraction boiling at 180～182° (3 mm.) was collected. The yield was 15.6 g. *Anal.* Calcd. for $C_{15}H_{14}ONCl$: C, 69.36; H, 5.44; N, 5.39. Found: C, 69.15; H, 5.36; N, 5.48.

N,N-Dimethylaminoacetone N-Benzyl-N-phenylhydrazone (XXI)——To N-benzyl-N-phenylhydrazine (9.9 g., 0.05 mole) and N,N-dimethylaminoacetone (5.1 g., 0.05 mole) was added acetic acid (0.5 ml.) after thorough mixing. After standing at room temperature for 1 hr., the mixture was partitioned between H_2O and benzene. The organic layer was separated, dried, and concentrated under reduced pressure. The hydrazone was obtained as an oil which formed a picrate, m.p. 94～95° (from EtOH). *Anal.* Calcd. for $C_{24}H_{26}O_7N_6$: C, 56.46; H, 5.13; N, 16.46. Found: C, 56.38; H, 5.17; N, 16.50.

The other compounds of Table IV were similarly prepared.

1-Benzyl-2-methyl-3-N,N-dimethylaminoindole (XXIX)——A mixture of N-benzyl-N-phenylhydrazine (9.9 g., 0.05 mole), N,N-dimethylaminoacetone (5.1 g., 0.05 mole), and acetic acid (0.5 mole) was heated for 1 hr. on a steam bath. After cooling the reaction mixture was extracted with benzene. The benzene extract was washed with H_2O, dried, and concentrated under reduced pressure. The residue was recrystallized from EtOH to yield 2.1 g. of colorless needles, m.p. 86°.

The other compounds of Table V were similarly prepared.

*2 All melting points were uncorrected.

4) S. Hauptman, *et al.*: Angew. Chem., **77**, 678 (1965).

When the portion insoluble in benzene was added to a small amount of EtOH and allowed to stand at room temperature for 3 to 7 days, 0.5 g. of methylglyoxal di-N-benzyl-N-phenylhydrazone separated. Recrystallization from EtOH gave an analytical sample as yellow prisms, m.p. 126°. *Anal.* Calcd. for $C_{29}H_{28}N_4$: C, 80.56; H, 6.48; N, 12.96. Found : C, 80.69; H, 6.47; N, 12.73.

Methylglyoxal Di-N-benzyl-N-phenylhydrazone——To a solution of 1.0 g. of 30% aqueous methylglyoxal was added 1.74 g. of N-benzyl-N-phenylhydrazine. The yellow precipitate was filtered and washed with H_2O. After recrystallization from EtOH it melted at 126°.

Methylglyoxal Diphenylhydrazone——A mixture of phenylhydrazine (3.3 g.) and N,N-dimethylaminoacetone (1 g.) was refluxed in 10 ml. of EtOH for 1 hr. on a steam bath. The reaction mixture was cooled and with 10 ml. H_2O added. The yellow precipitate was filtered, washed with H_2O and recrystallized from EtOH yielding 2 g. of methylglyoxal diphenylhydrazone, m.p. 148°, identified by comparison of its infrared spectrum with that of an authentic sample.[5]

The authors would like to express their deep gratitude to Dr. T. Akiba, director of this laboratory, for his encouragement throughout the course of this work. Thanks are also due to Mr. Tsuneo Ito, Kitazato University, for the NMR analysis.

5) H. V. Pechmann : Ber., **20**, 2539 (1887).

[Chem. Pharm. Bull. 15(1) 15 ~ 27 (1967)]

UDC 547.924.07

3. Katsumi Tanabe, Rinji Takasaki, Kiyoshi Sakai, Ryozo Hayashi, Yasuhiro Morisawa and Teruo Hashimoto : Steroid Series. XVI.*1 The Preparation of 3α,5α-Cyclo-6β,19-oxidosteroids and its Conversion to 19-Oxygenated Steroid Derivatives.*2

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3α,5α-Cyclo-6β,19-oxidosteroid (II) was synthesized by the lead tetraacetate oxidation of 3α,5α-cyclo-6β-hydroxysteroid (I) in benzene. The acid-catalysed solvolysis of the oxide (II) afforded 3α,5α-cyclo-19-hydroxy-6β-substituted steroid (XVI) and/or Δ^5-19-hydroxy-3β-substituted steroid (XVII), depending upon the reaction conditions employed. Oxidation of the oxide (II) with Jones reagent gave 3α,5α-cyclo-6β,19-dioxosteroid (XIX) with two equivalent molar oxidant, and 3α,5α-cyclo-6-oxosteroid-19-oic acid (XX) with the excess reagent.

(Received February 23, 1966)

The transannular substitution reaction to introduce a functional group at a suitably located, nonactivated carbon of the steroid nucleus has recently been employed by several groups[1] for preparation of the C-19 substituted steroid,[2] which is an useful

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