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The Reactions of N,N′-Diarylmethylenearylmethanediamine and Various Kinds of Compounds Containing Reactive Hydrogens

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Abstract: The finding that N,N′-diarylmethylenearylmethanediamine (1) condenses with various kinds of compounds containing an active hydrogen in the presence of ammonium acetate at mild conditions has led to the work extending the synthetic applications of the double Schiff base 1. As the results of the research on the reactions of 1 with various reactants, the many novel compounds shown in the text have been heretofore synthesized, and the pathways for their formations are estimated.

1. Introduction

Since it was noted as early as 1837[1] that benzaldehyde reacts with ammonia to afford the unique trimeric product, N,N′-dibenzylidenephenylmethanediamine (1a ; Ar=-C_6H_5) named also as hydrobenzamide[1], N,N′-dibenzylidenetoluene-α, α-diamine[2], 1-phenyl-N,N′-bis(phenyl-metylene)-methanediamine[3], α, α-bis(benzylideneamino) toluene[4] or 1,3,5-triphenyl-2,4-diaza-1,4-pentadiene[5], a number of analogous double Schiff bases has been reported[6,7,8]. These compounds contain two true ammono aldehyde group and one other group which is similar to the acetals in that two valence of the central carbon atom are satisfied by two nitrogen atoms rather than the same nitrogen atom. The double Schiff bases may also be considered as deammonation products of the imines (2), being related to the latter as the ethers are related to the alcohols and as the acid anhydrides are related to the acids.

$$3ArCHO + 3NH_3 \underset{+3H_2O}{\overset{-3H_2O}{\rightleftarrows}} \underset{\underline{2}}{3ArCH{=}NH} \underset{+NH_3}{\overset{-NH_3}{\rightleftarrows}} \underset{\underline{1}}{ArCH(N{=}CHAr)_2}$$

The nitrogen atom has one more electron than carbon and one less electron than oxygen. This simple fact, with the underlying arrangement of atomic orbitals, is at the origin that nitrogen atom has, in many respects, intermediate properties between the two atoms. Electronegativity was first induced by Pauling[9] as a semiquantitative concept. The

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values of his original electronegativities for these elements are C 2.5 (2.50), N 3.0 (3.07) and O 3.5 (3.50), where the numbers in brackets are the values by A. L. Allred[10,11]. The carbon-nitrogen double bond is also intermediate between the carbon-carbon double bond and carbon-oxygen double bond in many respects, and it is useful to compare the properties of these three groups which have certain analogies and differences.

The fundamental chemical and biological importance frequently comes of the possibility of having a lone pair in either a π^- or an sp^2 hybrid orbital on trigonally hybridized nitrogen, and it makes possible the formation of nitrogen containing molecules with the delicate differences in chemical properties related to the penomena of life. Thus, the azomethine group occurs in many fundamental important organic molecules or biologically active substances in vitro and vivo, and has been extensively studied. But, unexpectedly, open chain compounds with double carbon-nitrogen double bonds has received less attention apart from carbodiimides and azines.

Open chain compounds with double carbon-nitrogen double bonds have potential to be used extensively as reactants or reaction intermediate since one or both azomethine groups can take part in condensation reactions to give a variety of addition and heterocyclic compounds. Whereas, unfortunately, many of them with double carbon-nitrogen double bonds commonly show propensity to be polymerized with the other reactants or to be hydrolyzed. This is probably the main reason for less attension, in spite of the expectation for the utility to synthesis based on their unique structures.

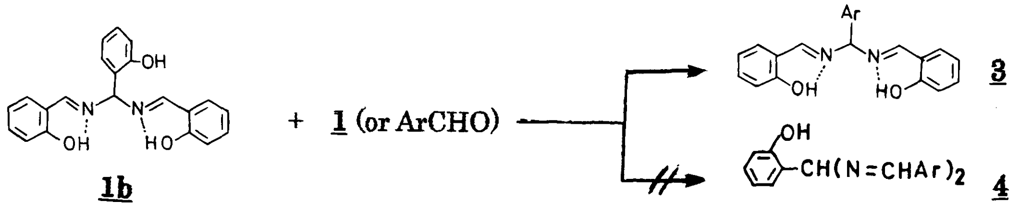
While, it happened to be found[12,13] that N,N′-bis[2-hydroxybenzylidene]-2- hydrophenylmethanediamine (**1b**; Ar=2-OH-C_6H_4) condenses with aliphatic ketones or aldehydes in the presence of abundant ammonium acetate at room temperature and the resulting pale yellow crystalline products were assigned to new heterocyclic system[13,14]. After this finding, in view of the possibility of synthetic application to nitrogen-containing heterocyclic compounds, the synthetic reactions of N,N′-diarylmethylenearylmethanediamines (1) with various kinds of compounds containing reactive hydrogens have been investigated.

2. Experimental

General: The melting points are measured with a Yamato melting point appatatus model MP-21. Microanalysis are take on a Yanagimoto C.H.N. Corder MT-2 instrument. The IR or FT-IR spectra are obtained with a Shimazu IR-27G type, a Hitach 260-30 type or a Nihonbunkou FT/IR-7300 type spectrophotometer. The ^{1}H-NMR spectra are recorded on a Nihondenshi JNM-MH-60 NMR spectrometer at 60 MHz and a Hitachi R-900 NMR spectrometer at 90 MHz, and sometimes on the other spectrometer at 100MHz. Spin decoupling are used for the assignments. The ^{13}C-NMR spectra are recorded on a Hitachi R-900 FT-NMR spectrometer at 22.6 MHz. Proton wide-band decoupling, off resonance decoupling, and gated (NOE) decoupling methods are used. The mass spectra were measured with a Hitachi M-52 single-focussing GC-MS mass spectrometer, using a direct insertion probe. The voltage for the electronbeam was 70 eV. The ionization chamber temperature was about 200 ℃.

Preparations of N,N′-Diarylmethylenearylmethanediamine (1) and N,N′-Bis[2- hydroxybenzylidene]arylmethanediamine (3) : The following five procedures (A)~(E) have been mainly used to prepare the various 1 ; (A) from aromatic aldehyde in liquid ammonia, (B) from aromatic aldehyde in concentrated aqueous ammonia, (C) from aromatic aldehyde and concentrated aqueous ammonia in ethanol or methanol, (D) from aromatic aldehyde in buffered solution of concentrated aqueous ammonia with ammonium chloride, (E) from aromatic aldehyde in solution of ammonium chloride, concentrated aqueous ammonia and ethanol.

The condensation product of salicylaldehyde and ammonia, N,N′-bis[2-hydroxybenzylidene]-2-hydroxyphenylmethanediamine (1b) reacts with several different arylaldehydes or other N,N′-diarylmethylenearylmethanediamine to give the new N,N′-bis[2-hydroxybenzylidene]arylmethanediamine (3)[15]. When a mixture of 2 mol of 1b and 3 mol of an arylaldehyde is allowed to react in the presence of 2 mol of ammonium acetate in methanol, various sorts of 3 are formed in good yields[15]. Compound (3) can also be prepared under the same conditions from 1b and other N,N′-diarylmethylenearylmethanediamine. On the other hand, in this reaction none of N,N′-diarylmethylene-2-hydroxyphenylmethanediamine (4) could be detected[15].

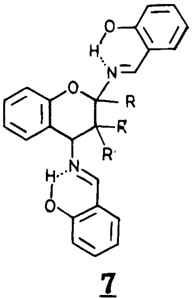


General Method for the Reactions of N,N′-diarylmethylenearylmethanediamine (1) and Compounds Containing an Active Hydrogen: An equivalent mixture of N,N′-diarylmethylenearylmethanediamine (1), the compounds containing reactive hydrogens and ammonium acetate in methanol was stirred at ambient temperature.

3. Results and Discussion

Synthesis of 2N,4N-Bis[2-hydroxyphenylmethylene]-2,3-dihydro-4H-benzopyran-2,4-dia-

mines (7) : The reaction of 1a and an aryl aldehyde gives yellow solids, N,N′-bis[2-hydroxybenzylidene]arylmethanediamine (3). Similar treatments of 1a and aliphatic aldehyde (5;R^1=H) afford yellow crystalline products, which are not the expected N,N′-bis[2-hydroxybenzylidene]alkylmethanediamines (6) but determined as 2N,4N-bis[2-hydroxyphenylmethylene]-2,3-dihydro-4H-1-benzopyran-2,4-diamines[16,17] (7). The double Schiff base 1a and aliphatic ketones, 1-acetyladamantane, bicyclo- [3.2.1]octan-2-one, cyclanones, α-tetralones, thiochroman-4-one, 1-benzosuberone, cycloalkyl phenyl ketones, 2-acetylbutyrolacetone, 2-acetyl-1-tetralone, etc reacted similarly to give novel benzopyran derivatives[14], for example, such as shown following.



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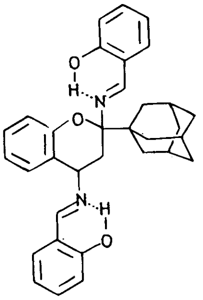
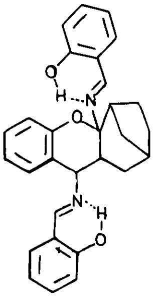
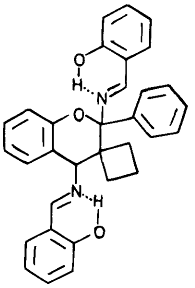
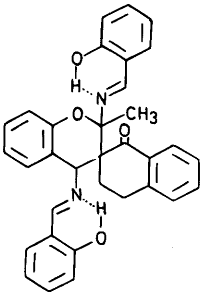
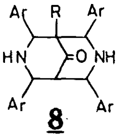








Synthesis of Heterocyclic Compounds from N,N′-Diarylmethylenearylmethanediamine and Ketones: To obtain the guide of the reactivity of various aldehydes and ketones for 1 expect for 1b or the analogs , at first as a general method, an equivalent mixture of 1a, the carbonyl compound and ammonium acetate in methanol was stirred at ambient temperature. As the results, 1a showed to be unreactive to aldehydes, but showed multifarious reactivity to many aliphatic ketones containing α-hydrogen. For example, 2,4,6,8-tetraphenyl-3,7-diazabicyclo[3.3.1]nonan-9-one (8a), 8,8-dimethyl-2,4,5,7-tetraphenyl-2,3,4,4a,5,6,7,8-octahydropyrido[4,3-d]pyrimidine (9a) and 4-tert-butyl-2,6,8,9-tetraphenyl-1,3,7-triazabicyclo[3.3.1]non-3-ene (10a) from the reaction of 1a with acetone, isopropyl methyl ketone, or tert-butyl methyl ketone, respectively, and ammonium acetate in methanol. With ethyl methyl ketone, a mixture of products 8b and 9a was obtained. As the intermediates on the formations of 8b, 9a and 9b, 3-methyl- and 3,3-dimethyl-2,6-diphenyl-4-piperidone (11a and 11b) were isolated. Moreover, 2,4,6,8,9-pentaphenyl-1,3,7-triazabicyclo[3.3.1]-3-nonene (12a), 5,5-dimethyl- 2,4,6-triphenyl-2,3,4,5-tetrahydropyrimidine (13a), 2,4-diphenyl-6-(2-hydroxyphenyl)-2,3,4,5- tetrahydropyrimidine (13b), 5-acetyl-2,6-diphenyl-4-methyl-1,2,3,6-tetrahydropyrimidine (14a), N-benzylidene-1-phenyl-2-acetyl-2-benzoylethylamine (15a), N-benzylidene-α-(1-phenancylcyclopentylidene)-α-phenylmethylamine (16a), 1-methyl -2,4-diphenyl- 3-azabicyclo[3.3.1]nonan-9-one (17a), 5-methyl-2,4,5,7-tetraphenyl-3,4,5,6,7,8-hexahydro-2H-4a,8-propanopyrido[4,3-d]pyrimidene (18a), 2,4-diphenyl-2,3,4,4a,5,6-hexahydrobenzo[h]quinazoline (19a) and 1H-indeno[1,2-f]-3,6a-methano-2,4,6,12-tetraphenyl-2,3,4,5,6,6a-hexahydro-1,3,5-triazocine (20a) were synthesized from the analogous condensations of 1a with acetophenone, isopropyl phenyl ketone, 2-hydroxyphenyl methyl ketone, acetylacetone, 1-phenyl-1,3-butanedione, cyclopentyl phenyl ketone, 2-methylcyclohexanone, α-tetralone and 1-indanone, respectively[17-23].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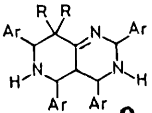
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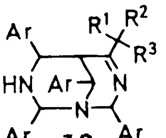
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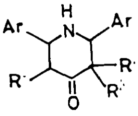
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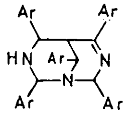
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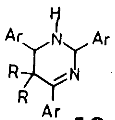
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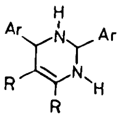
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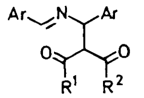
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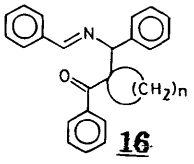
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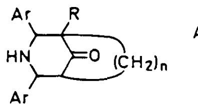
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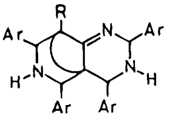
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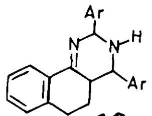
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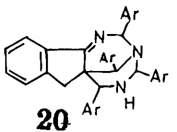
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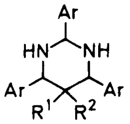
Synthesis of Perhydropyrimidines and piperidines through the double Michael Addition of Some Aactive Methylene Compounds to N,N′-Diarylmethylenearylmethanediamine 1: The synthesis of hexahydropyrimidines (21) from the double Michael addition reactions of active methylene compounds to both azo- methine groups of 1 is achieved by using malononitrile, nitromethane, nitroethane, methyl cyanoacetate, α-cyanoacetamide. 1,3-Indandion also reacts to afford spiro[1,3-indanedione-2,5′- (1′,2′,3′,4′-tetrahydro-2′,4′,6′-triaryl)-pyrimidine] (22).

Triarylpiperidines (23) and N-arylidenemethylamines (24) are synthesized by similar treatment of the active methylene and active methane compounds with 1[24].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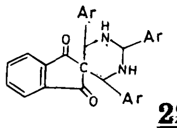
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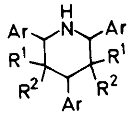
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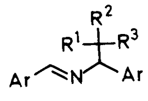
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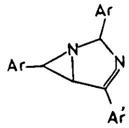
Synthesis of 1,3-Diaza-, and 1,3,5-Triazabicyclo[3.1.0]hexanes using N,N′-Diarylmethylenearylmethanediamine: The 1,3-diazabicyclo[3.1.0]hex-3-enes (25) are formed by the reaction of 1 with phenacyl chloride or phenacyl bromide in methanol containing ammonium acetate at ambient temperature. The formation of 25 by phenacyl bromide occurred more readily than by phenacyl chloride. The reaction is believed to be initiated by the Michael reaction between 1 and phenacyl halides. The removal of one molecule of aryl aldehyde from the adduct leads to the formation of 2,3,4,5-tetrahydropyrimidines (13), which split off hydrogen halide to produce 25. Similar treatment of 1 with α,α-dichloroacetophenone, desyl chloride, methyl ether or benzoyl acetonitrile did not give 25 but 2,3,4,5-tetrahydropyrimidines (13), 2-aza-1,3-butadienes (26) or 3,5-dicyano- 3,5-dibenzoyl -2,4,6-triphenylperhydropyridine (23).

While, when a mixture of 1a, benzoyl peroxide, and ammonium acetate in methanol was stirred at ambient temperature, 2,4,6-triphenyl-1,3,5-triazabicyclo[3.1.0]hexane (27a) was formed in 40 % yield[25,26].



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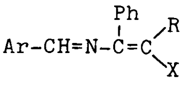
$Ar\text{-}CH{=}N\text{-}\overset{Ph}{C}{=}C(R)X$

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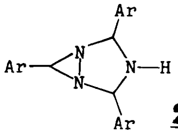

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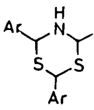
Synthesis of 1,3,5-Dithiazines, N-Arylmethylene-1-thioacylamino-1-arylmethylamine and Hexahydro-1,3,5-triazine-2-thions using N,N′-Diarylmethylenearylmetananediamine: The reaction of 1 with thioamide or thiopropionamide in the presence of ammonium acetate in methanol gave 2,4,6-triaryl-5,6-dihydro-2H,4H-1,3,5-dithiazine (28). Whereas the reaction of 1 with thioamides in an aprotic solvent such as benzene or acetonitrile at 70 ℃ yielded N-arylmethylenethioacylamino-1-arylmethylamine (29) as major product. The production of 28 in protic solvent was considered as following; the initial step is the Michael type addition of thioamides of thiol type to the azomethine group of 1, followed by elimination of aldimine from adduct, once again the addition of thioamides, elimination of RCN, and then cyclocondensation of the resultant intermediate with aldimine to 28. Similarly, 1-(1,3-diaryl-2-aza-2-propenyl)-2-imidazolidones (30) and 1,3-bis(1,3-diaryl-2-aza-2-propenyl)-2-imidazolidones (31) were prepared from the condensation of ethylenethiourea or ethyleneurea with 1. The reactions of the other thioureas, isothiocyanates and ureas such as allylthiourea, ethyl isothiocyanates, benzyl isothiocyanate, methylurea, and allylurea with 1 afforded tetrahydro-1-substituted-4,6-diaryl-1,3,5-triazine-2(1H)-ones (32) and N-(1,3-diaryl-2-aza-2-propenyl)-N′-substituted-ones (33)[26].



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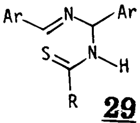

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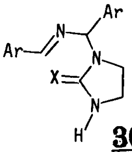

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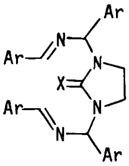

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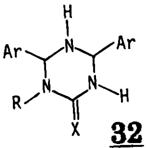

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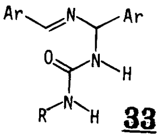

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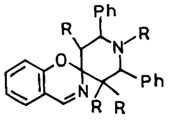
Other Unique Synthetic Reactions on N,N′-Diarylmethylenearylmethanediamine: It was expected that 1b would react with 4-piperidones (11) to give 2,3-dihydro-4H-benzopyran-2,4-diamine derivatives 7. However, compounds 7 could not be isolated and spiro[2H-1,3-benzoxazine-2,4′-piperidines] 34 and 4-tetrahydropirimido-2-arylmethyleneamines 35 were obtained from the above mentioned reactions[27].



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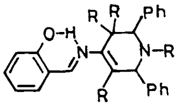
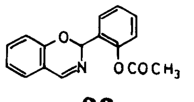


35

The acetylation of 1b were carried out with acetic anhydride, acetic acid, acetic anhydride, piperidine-acetic anhydride, pyridine-acetyl chloride and others in usual ways. The reactions did not afford the desired N,N′-bis[2-acetoxybenzylidene]-2-acetoxyphenylmethanediamine, but 2-(2-acetoxyphenyl)-2H-1,3-benzoxazine (36), 2-(2-acetoxyphenyl)-4-acetylamino-3,4-dihydro-2H-1,3-benzoxazine (37), 2-(2-acetoxyphenyl)-4-diacetylamino-3,4-dihydro-2H-1,3-benzoxazine (38) and sometime as by-product, tricyclo-3,4-dihydro-2H-1,3-benzoxazine (39) were obtained[28].



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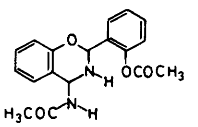

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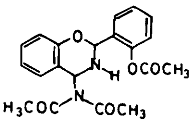

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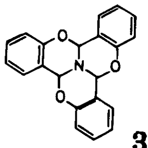
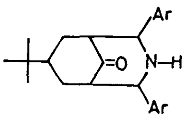


39

The condensation of 1 with cyclohexanone gave polymeric resin product and didn′t yield crystalline matters. Whereas, similar treatment of 1 and 4-tertbutylcyclohexanone produced 7-tert-butyl-2,4-diaryl-3-azabicyclo[3.3.1]nonan-9-one (40) and 8-arylmetylene-6-tert-butyl-2,4-diaryl-1,2,3,4,5,6,7,8-octahydroquinazoline (41).



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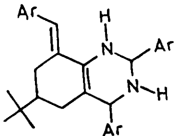
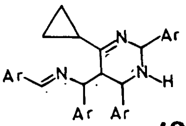
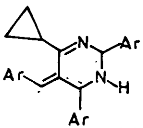


41

Cyclopropyl phenyl ketone was unreactive to 1. While, cyclopropyl methyl ketone reacted with 1, and gave the cyclopropyl derivatives of 7, 10, 5-[N-(arylidene)-α-amino-α-arylmethyl]-6-cyclopropyl-2,4-diaryl-2,3,4,5-tetrahydropyrimidine (42) and 5-arylmethylene-6-cyclopropyl-2,4-diaryl-2,3,4,5-tetrahydropyrimidine (43).

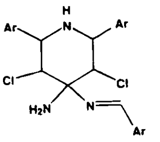


42

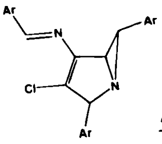


43

The double Schiff base 1 and 1,3-dichloro-2-propanone afford the condensation products from which three crystal compounds are isolated. The two crystal compounds are determined to be 4-amino-4-(N-arylideneamino)-3,5-dichloro-2,6-diarylpiperidine (44) and 4-(N-arylideneamino)-3-chloro-2,6-diaryl-1-azabicyclo[3.1.0]hex-3-ene (45)[29].



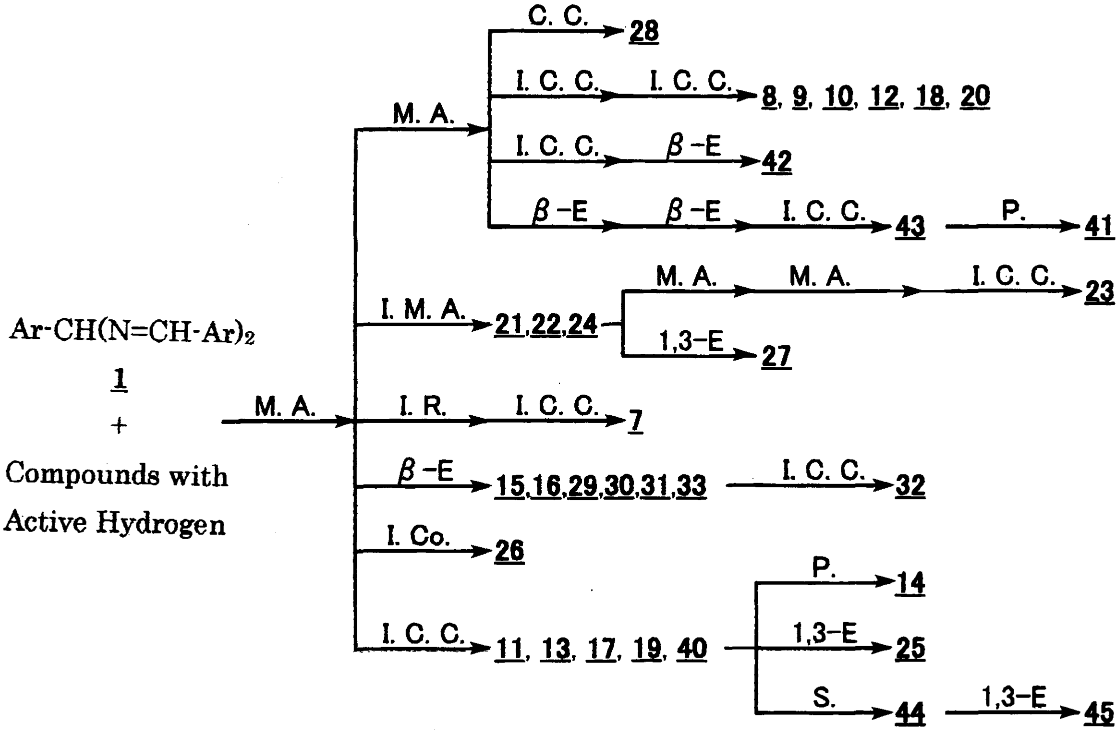
44



45

The reactions of N,N′-bis(2-hydroxybenzylidene)-2-hydroxyphenylmethanediamine (1b) with various aldehydes and ketones containing an α-hydrogen atom, and 3,3-dimethyl-2,4-diaryl-4-piperidones give 3, 7 and 34, respectively. The cyclocondensation of 1b by carboxylic acids affords 39. On the other hand, the products of two types (21 and 23), eleven types (8~25, 39 and 41), 27, two types (28 and 29), and two types (31 and 32) are obtained from the condensations of 1 (except 1b) with active methylene compounds, ketones containing α-hydrogen atoms, benzoyl peroxide, thioamides, thioureas, and ureas, respectively.

The reactions for the formations of 21~32, 39 and 41 are believed to be initiated by the intermolecular Michael type addition between the double Schiff base 1 as acceptors and compounds with active hydrogen atoms as donors, and then it could be considered the following path ways which contain the intramolecular Michael type addition, intermolecular cyclocondensation, intramolecular cyclocondensation, β-elimination, prototropy, intramolecular rearrangement, intramolecular condensation, and substitution.



M. A. ; Intermolecular Michael Type Addition
I. M. A. ; Intramolecular Michael Type Addition
C. C. ; Intermolecular Cyclocondensation
I. C. C. ; Intramolecular Cyclocondensation

β-E ; β-Elimination
P. ; Prototropy
I. R. ; Intramolecular Rearrangement
I. Co. ; Intramolecular Condensation
S. ; Substitution

These results also indicate that the compounds containing the reactive functional groups such as X-H (X=C, N, O, S), -NH$_2$, -NH-C(=X)-NH- (X=O, S), CH$_2$, -C(=O)-CH, -C(=O)-CH$_2$-, -C(=O)-CH$_3$, -CH-C(=O)-CH-, CH-C(=O)-CH$_2$-, -CH$_2$-C(=O)-CH$_2$-, -C(=O)-CHX- (X=Cl, Br), -C(=O)-, and -CHCl -C(=O)-CH$_2$Cl have potential as reagents for the synthesis of the majority of **3**~**45**, as shown in the following.

X-H (X=C, N, O, S)	; **28**, **29**, **30**, **31**, **33**
-NH$_2$	; **27**
-NH-C(=X)-NH-	; **32**
-CH$_2$-	; **21**, **22**, **23**
-C(=O)-CH	; **7**, **10**, **11**, **13**, **15**, **16**, **19**, **35**
-C(=O)-CH$_2$-	; **12**, **14**, **20**, **42**
-C(=O)-CH$_3$	; **41**, **43**
CH-C(=O)-CH	; **17**, **40**, **44**
CH-C(=O)-CH$_2$-	; **9**, **18**
CH2-C(=O)-CH$_2$-	; **8**, **39**
-C(=O)-CHX- (X=Cl, Br)	; **25**
-C(=O)-	; **3**, **34**
-CHCl-C(=O)-CH$_2$Cl	; **45**

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