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New β-Adrenoreceptor Stimulants. Studies on 3-Acylamino-4-hydroxy-α-(N-substituted aminomethyl)benzyl Alcohols[1)]

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New β-adrenergic stimulants, 3-acylamino-4-hydroxy-α-(N-substituted aminomethyl)-benzyl alcohols (VIII) were prepared *via* 3-amino-4-benzyloxy-α-(N-substituted aminomethyl)benzyl alcohols (V) in several steps. These agents were catecholamine derivatives, in which *m*-phenolic OH was replaced by acylamino and substituted acylamino groups. Terbutaline analogues (XIXa, b, XX), in which one or both of two phenolic OH were replaced by formamido or methoxycarboxamido groups were synthesized, too. Compounds (VIIIa, c, l—q) bearing formylamino group in the *meta* position showed potent β_2-stimulant activity *in vitro*. In these, N-phenylalkyl series were more potent β_2-stimulant than N-alkyl series. Several compounds, which bear two asymmetric centers, were separated into two racemates and the β_2-stimulant activity of them were different. From these compounds, 3-formamido-4-hydroxy-α-(N-(*p*-methoxy-α-methylphenethyl)aminomethyl)-benzyl alcohol ·1/2 fumarate (VIIIn-A) (BD-40-A) was selected as the best compound.

Keywords——bronchodilator; benzyl alcohol; β-stimulant; diastereoisomers; structure-activity relationship; isolated guinea-pig trachea; BD-40-A

Isoproterenol, a potent β-adrenergic agonist, is widely used clinically as a bronchodilator; however, it is nonselective β-stimulant which is active in stimulating the heart as well as in dilating the bronchial muscle. In addition, it lacks oral activity and long duration of effect because of rapid inactivation due to the formation of ineffective metabolites (*o*-sulfate, *o*-methylether).[3)] The search for improved bronchodilators has centered on compounds which have higher degree of selectivity on bronchial muscle, oral efficacy and longer duration of effect.

The studies of chemical manipulations of isoproterenol have demonstrated that *m*-phenolic function may be replaced with a variety of functionalities capable of undergoing hydrogen bonding, *e. g.*, soterenol,[4)] salbutamol,[5)] carbuterol,[6)] sulfonterenol.[7)] These compounds obtained by such modifications are the improved bronchodilators with bronchial selectivity and oral activity. Resorcinol type of compounds represent another examples of the structural modification and include orciplenaline,[8)] terbutaline,[9)] fenoterol.[10)] These have also been reported to be improved bronchodilators. An analogue of terbutaline, in

1) *a*) A part of this work was presented at the 95th Annual Meeting of the Pharmaceutical Society of Japan, Nishinomiya, April 1975; *b*) Yamanouchi Pharmaceutical Co. Ltd., Ger. Patent 2305092 (1973) [*C.A.*, **79**, 126063 (1973)].
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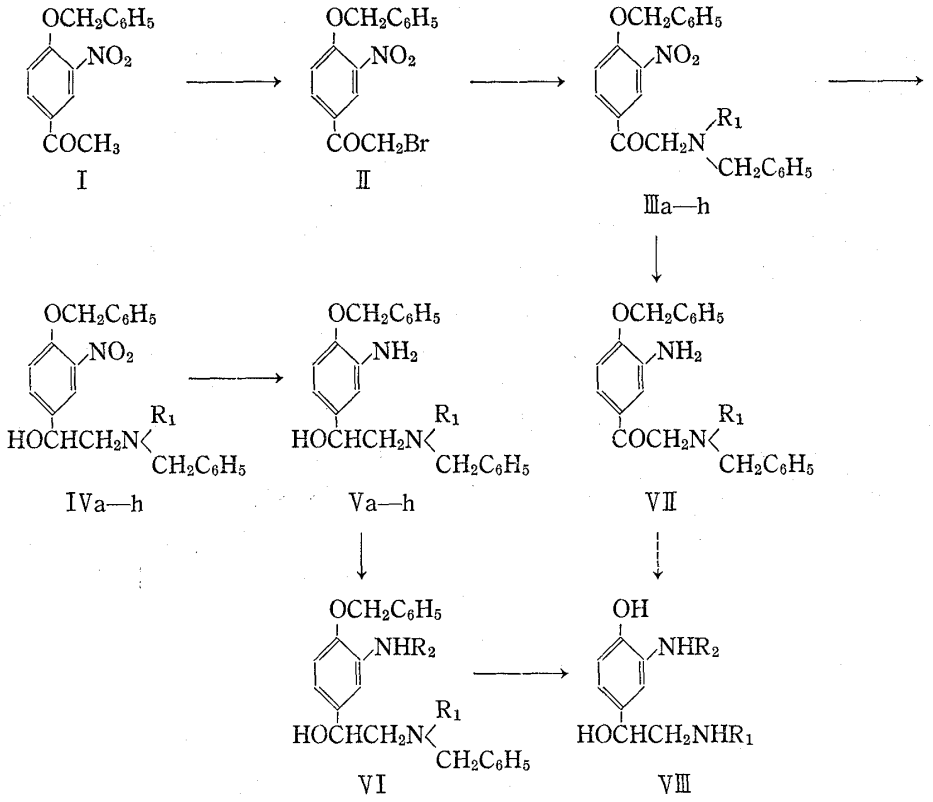
9) J. Bergman, H. Persson, and K. Wetterlin, *Experientia*, **25**, 899 (1969).
10) M.J. Mattila, A. Muittari, and H. Tiitinen, *Arzneimittels-Forsch.*, **17**, 362 (1967).

which phenolic OH was replaced by hydroxymethyl function, is reported to have selective β_2-stimulant activity, but to be less potent than terbutaline.[11]

In a search for selective and potent bronchodilators, we examined a series of catecholamine derivatives in which the *m*-phenolic OH was replaced by acylamino[12] and substituted acylamino groups containing two mobile protons. The analogue of terbutaline, in which one or both of two phenolic OH were replaced by formamido or methoxycarboxamido groups was studied, too. In this report are described the synthesis and results of preliminary pharmacological study of these compounds.



Compd. No.	R_1	Compd. No.	R_1
IIIa, IVa, Va	$CH(CH_3)_2$	IIIe, IVe, Ve	$CH(CH_3)CH_2C_6H_4OCH_3$-(*p*)
IIIb, IVb, Vb	$C(CH_3)_3$	IIIf, IVf, Vf	$CH(CH_3)CH_2CH_2C_6H_4OH$-(*p*)
IIIc, IVc, Vc	$CH(CH_3)CH_2C_6H_4CH_3$-(*p*)	IIIg, IVg, Vg	$CH(CH_3)CH_2CH_2$-c-C_6H_{11}
IIId, IVd, Vd	$CH(CH_3)CH_2C_6H_4OH$-(*p*)	IIIh, IVh, Vh	$C(CH_3)_2CH_2C_6H_5$

Chart 1

3-Acylamino-4-hydroxy-α-(N-substituted aminomethyl)benzyl alcohols generally have been synthesized *via* 3′-acylamino-4′-benzyloxy-2-bromoacetophenones,[4,6] but we selected 3-amino-4-benzyloxy-α-(N-substituted aminomethy)benzyl alcohols (V) as a keyintermediate in the synthesis of 3-acylamino-4-hydroxy-α-(N-substituted aminomethyl)benzyl alcohols (VIII) for the following two reasons. 1) In case of the acylamino groups which are labile in acid (*e.g.*, formylamino and N-formylglycylamino groups), the bromination of 3′-acylamino-4-′-benzyloxyacetophenones with bromine was accompanied with deformylation. 2) A series of substances (VIII) appeared to be obtained easily by the acylation of V with a variety of acylating agents followed by catalytic hydrogenation.

11) C.F. Schwender, B.R. Sunday, and J. Shavel, Jr., *J. Med. Chem.*, **17**, 1112 (1974).
12) In reference 6, two compounds, 3-formamido-4-hydroxy-α-(N-*tert*-butylaminomethyl)benzyl alcohol and 3-acetamido-4-hydroxy-α-(N-*tert*-butylaminomethyl)benzyl alcohol are reported to have potent and selective tracheal relaxant property.

4′-Benzyloxy-3′-nitroacetophenone (I) was converted to 4′-benzyloxy-3′-nitro-2-bromoacetophenone (II)[6] by bromination with bromine in chloroform in 85% yield. II was condensed with an appropriate N-benzyl-N-substituted amine to afford 4′-benzyloxy-3′-nitro-2-substituted aminoacetophenones(IIIa—h), as shown in table III. IIIa—h were reduced with $NaBH_4$ in ethanol (or ethanol–chloroform) to give 4-benzyloxy-3-nitro-α-(N-substituted aminomethyl)benzyl alcohols (IVa—h) quantitatively. The nitro compounds (IVa—h) were treated with reduced iron powders and hydrochloric acid in 80% methanol to give 3-amino-4-benzyloxy-α-(N-substituted aminomethyl)benzyl alcohols (Va—h) in 80—90% yield, in which only nitro groups were reduced selectively. The reduction of the aminoketone (IIIb) to 3′-amino-4′-benzyloxy-α-(N-benzyl-N-*tert*-butylaminomethyl)benzyl alcohol (VII) was examined under the same condition as the reduction of IV, but not successful resulting in darkbrown products which were complex mixtures. The reduction of IIIb was also examined by catalytic hydrogenation in the presence of Raney-nikel at room temperature, however, the reduction of a nitro group of IIIb to an amino group was accompanied with debenzylation making it difficult to obtain pure VII without purification by chromatography. Consequently, a series compounds (VIII) were synthesized *via* aminoalcohols (V). Va—h were acylated with a variety of acylating agents to give N,O-diacylated compounds, which were selectively hydrolyzed under basic conditions to give 3-acylamino-4-benzyloxy-α-(N-substituted aminomethyl)benzyl alcohols(VIa—r), as shown in Table IV. VIa—r were hydrogenated in the presence of 10% Pd–C in ethanol (or isopropanol) to give 3-acylamino-4-hydroxy-α-(N-substituted aminomethyl)benzyl alcohol (VIIIa—r), as shown in Table I.

All compounds reported in this paper contain at least one asymmetric carbon atom. Several compounds (VIIIl-p, VIIIr) have one additional asymmetric carbon atom located

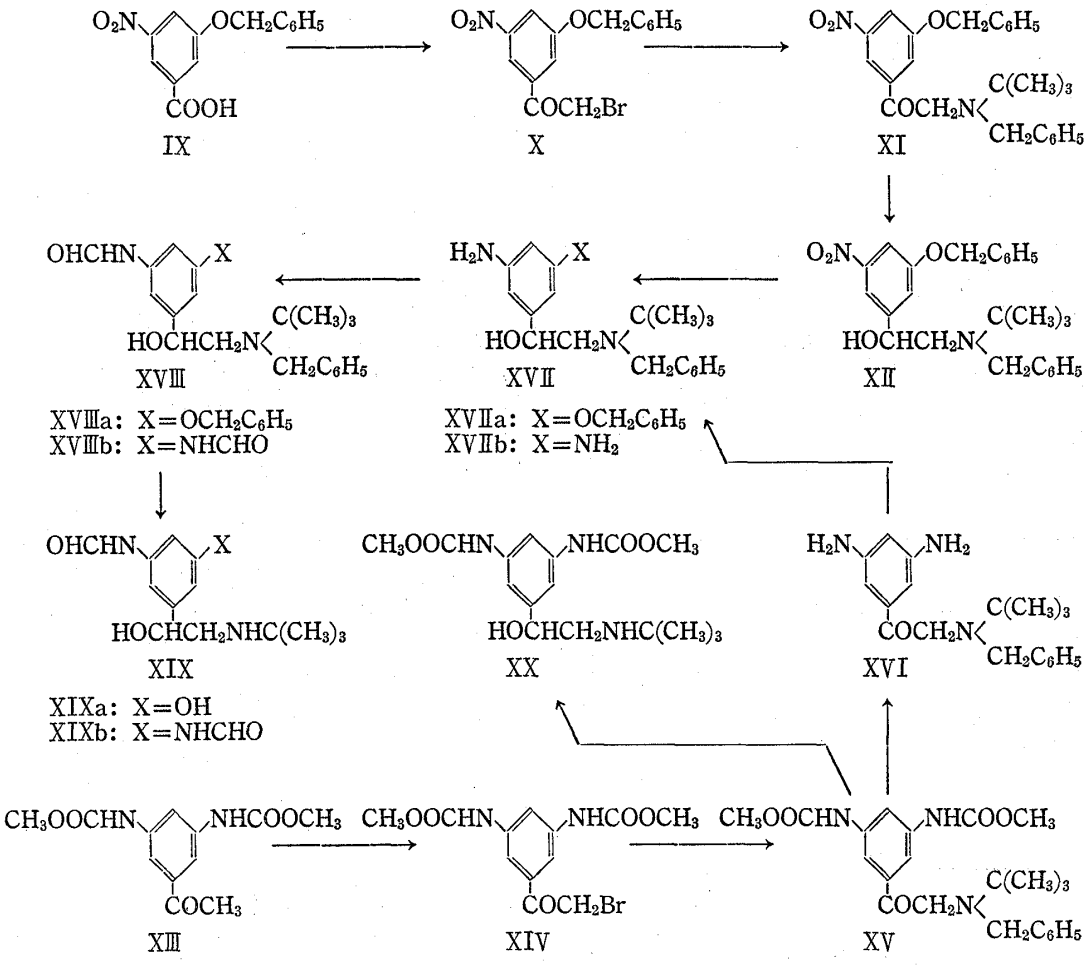
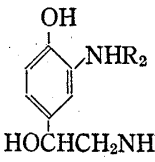


Chart 2

in the amine moiety and in those two pairs of enantiomers (two recamates) are possible. The two racemates were distinguishable from each other from the differece of nuclear magnetic resonance (NMR) spectra, signal patterns of methylene(2H) of N-benzyl group, of the syn-

TABLE I. 3-Acylamino-4-hydroxy-α-(N-substituted aminomethyl)benzyl Alcohols



Compd. No.	R_1	R_2	Salt	mp (°C)	Recrystn solvent	Yield (%)	Formula	Analysis (%) Calcd. (found) C	H	N
VIIIa	$CH(CH_3)_2$	CHO	½fumarate	180	EtOH	69	$C_{14}H_{20}O_5N_2$	56.75 (56.71)	6.80 (6.76)	9.45 (9.70)
VIIIb	$CH(CH_3)_2$	$COCH_3$	½fumarate	192	EtOH	42	$C_{15}H_{22}O_5N_2$	58.05 (57.98)	7.15 (7.15)	9.03 (9.09)
VIIIc	$CH(CH_3)_2$	$COCH_2OH$	HCl	190	MeOH–ether	46	$C_{13}H_{21}O_4N_2Cl$	51.23 (50.79)	6.95 (7.03)	0.19 (9.03)
VIIId	$C(CH_3)_3$	CHO	½fumarate	196[a]	EtOH	67	$C_{15}H_{22}O_5N_2$	58.05 (58.03)	7.15 (7.21)	9.03 (8.94)
VIIIe	$C(CH_3)_3$	$COCH_2NHCHO$	½fumarate	201	EtOH	63	$C_{17}H_{25}O_6N_3$	55.57 (55.42)	6.86 (7.00)	11.44 (11.30)
VIIIf	$C(CH_3)_3$	$COCH_2NHCOCH_3$	½fumarate	192	90%iso-PrOH	73	$C_{18}H_{27}O_6N_3$	56.68 (56.37)	7.14 (7.41)	11.02 (10.81)
VIIIg	$C(CH_3)_3$	$COCH_2CH_2NHCHO$	CH_3COOH	140	EtOH–ether	38	$C_{18}H_{29}O_6N_3 \cdot \frac{1}{2}H_2O$	55.09 (54.96)	7.71 (7.51)	10.71 (10.51)
VIIIh	$C(CH_3)_3$	$COCH_2CH_2OH$	HCl	202	EtOH–ether	68	$C_{15}H_{25}O_4N_2Cl$	54.13 (53.93)	7.57 (7.38)	8.42 (8.06)
VIIIi	$C(CH_3)_3$	$CO(CH_2)_3NHCHO$	½fumarate	197	EtOH	72	$C_{19}H_{29}O_6N_3$	57.71 (57.42)	7.39 (7.42)	10.63 (10.37)
VIIIj	$C(CH_3)_3$	COC_6H_4OH-(*p*)	½fumarate	202	EtOH	52	$C_{21}H_{26}O_6N_2$	62.67 (62.56)	6.51 (6.47)	6.96 (7.10)
VIIIk	$C(CH_3)_3$	COC_6H_4OH-(*m*)	½fumarate	180	EtOH	74	$C_{21}H_{26}O_6N_2$	62.67 (62.34)	6.51 (6.45)	6.96 (6.68)
VIIIl A	$CH(CH_3)CH_2C_6H_4CH_3$-(*p*)	CHO	½fumarate	127	80%iso-PrOH	70	$C_{21}H_{26}O_5N_2 \cdot H_2O$	62.36 (62.42)	6.98 (6.74)	6.93 (6.94)
VIIIl B			½fumarate	128	80%iso-PrOH	59	$C_{21}H_{26}O_5N_2 \cdot H_2O$	62.36 (62.52)	6.98 (6.81)	6.93 (6.98)
VIIIm A	$CH(CH_3)CH_2C_6H_4OH$-(*p*)	CHO	½fumarate	153	95%iso-PrOH	80	$C_{20}H_{24}O_6N_2 \cdot H_2O$	59.10 (58.98)	6.45 (6.33)	6.89 (6.74)
VIIIm B			½fumarate	155	95%iso-PrOH	80	$C_{20}H_{24}O_6N_2 \cdot H_2O$	59.10 (59.17)	6.45 (6.36)	6.89 (6.86)
VIIIn A	$CH(CH_3)CH_2C_6H_4OCH_3$-(*p*)	CHO	½fumarate	140	95%iso-PrOH	81	$C_{21}H_{26}O_6N_2 \cdot H_2O$	59.99 (59.63)	6.71 (6.65)	6.66 (6.71)
VIIIn B			½fumarate	155	95%iso-PrOH	48	$C_{21}H_{26}O_6N_2 \cdot \frac{2}{3}H_2O$	60.89 (60.94)	6.65 (6.69)	6.76 (6.77)
VIIIo-A	$CH(CH_3)CH_2CH_2C_6H_4OH$-(*p*)	CHO	½fumarate	147	95%iso-PrOH	80	$C_{21}H_{26}O_6N_2 \cdot H_2O$	59.99 (60.07)	6.71 (6.81)	6.66 (6.74)
VIIIp-A	$CH(CH_3)CH_2CH_2$-c-C_6H_{11}	CHO	CH_3COOH	140	95%iso-PrOH	67	$C_{21}H_{34}O_5N_2$	63.94 (64.33)	8.69 (8.92)	7.10 (7.36)
VIIIq	$CH(CH_3)_2CH_2C_6H_5$	CHO	½fumarate	145	MeOH–ether	75	$C_{21}H_{26}O_5N_2 \cdot H_2O$	62.36 (62.79)	6.98 (7.01)	6.93 (6.71)
VIIIr-A	$CH(CH_3)CH_2C_6H_4OH$-(*p*)	$COCH_2NHCOCH_3$	CH_3COOH	[b]						

a) Reference 7 reports mp 192—193° for the hydrochloride.
b) An amorphous solid. NMR(D_2O) δ: 0.99 (3H, d, >CHC$\underline{H}_3$), 1.86 (3H, s, –COCH_3), 2.60 (2H, m, –C$\underline{H}_2$C$_6$H$_4$OH(*p*)), 2.98 (2H, m, –CH(OH)C$\underline{H}_2$–), 3.85 (2H, s, –COCH_2N<), 6.50—7.40 (7H, aromatic protons)

thetic intermediates, IV, V and VI, of VIII. One of racemates showed an AB-quartet type at δ 3.4—3.5(1H) and 3.7—3.9(1H), the other showed a singlet type at δ 3.65—3.80(2H). The former was designated isomer-A[13] and the latter was designated isomer-B.[13] The isomers were not distinguishable from each other by NMR spectrum of VIII, itself. The reduction of aminoketones (IIIc—g) by $NaBH_4$ in ethanol affords a mixture of isomer-A and isomer-B, with the isomer-A being the major product. The ratio of isomer-A to isomer-B of IVd was 3:2 and those of IVf, g, containing more bulky amine moieties than IVd, were about 3:1. The separation of two racemates was made by the selective crystallization of either racemate from solution of two racemates in approprite solvent or the chromatography using silica gel.

Terbutaline analogue, XIXa, b, XX, in which one or both phenolic OH groups of terbutaline were replaced by formamido, methoxycarboxamido groups, were prepared as outlined in Chart 2. 3-Formamido-5-hydroxy-α-(N-*tert*-butylaminomethyl)benzyl alcohol (XIXa) was prepared *via* 3-amino-5-benzyloxy-α-(N-benzyl-N-*tert*-butylaminomethyl)benzyl alcohol (XVII) from the bromoketone (X) in the same sequence of reactions as the preparation of VIII from II. Condensation of 3′, 5′-bis(methoxycarboxamido)-2-bromoacetophenone (XIV) and N-benzyl-N-*tert*-butylamine gave the aminoketone (XV) which upon hydrogenolysis afforded 3,5-bis(methoxycarboxamido)-α-(N-*tert*-butylaminomethyl)benzyl)-benzyl alcohol (XX). XV was heated in conc. HBr to give 3′,5′-diamino-2-(N-benzyl-N-*tert*-butylamino)acetophenone (XVI). The reduction of XVI with $NaBH_4$ gave the aminoalcohol (XVIIb), which was formylated and then hydrogenated over Pd-C(10%) to yield 3,5-bis(formamido)-α-(N-*tert*-butylaminomethyl)benzyl alcohol(XIXb).

Table II. Relative Bronchodilator Potencies[a]
(Dose Ratios, Isoproterenol=1.0)

Compd.	Antihistamine	Antimethacholine
Isoproterenol	1.0	1.0
VIIIa	0.8	5.6
VIIIb	210	>300
VIIIc	>500	>300
VIIId	0.6	1.2
VIIIe	>500	>300
VIIIf	42	>300
VIIIg	>500	>300
VIIIh	35	>300
VIIIi	3.1	>300
VIIIj	230	>300
VIIIk	21	>300
VIIIl-A	0.3	3.6
VIIIl-B	2.7	25
VIIIm-A	0.2	0.3
VIIIm-B	0.75	2.3
VIIIn-A	0.1	0.1
VIIIo-A	0.2	0.2
VIIIp-A	1.0	28
VIIIq	0.5	>300
VIIIr-A	27	40
XIXa	>500	>300
XIXb	>500	>300
XX	>300	>300

a) based on the effective dose required to give 50% relaxation of histamine- and methachloline- induced constriction of isolated guinea-pig tracheal preparations

13) An attempt is being made to determine the absolute configuration of VIIIn-A.

New compounds were tested for broncholytic effect against histamine- or methacholine-induced broncho-constriction of isolated guinea-pig trachea. The data were summarized in Table II. Compounds (VIIIa,d,l—o) bearing formamido group in the *meta* position showed potent β_2-adrenergic stimulant activities. In these, N-phenylalkyl series (VIIIl—o) were more potent (bronchodilators) than N-alkyl series (VIIIa,d) as seen with known compounds. The diastereoisomer-A was several times as potent as isomer-B. This result shows that the configuration of the amine moiety in N-phenylalkyl series having an asymmetric carbon atom plays an important role in β-stimulant activities. Any compounds of XIXa, b, XX, terbutaline analogues, were very weakly effective as relaxants of the trachea. VIIId, VIIIl—o with sufficient potency were evaluated in a variety of additional systems. Compounds (VIIIl—o) exhibited high degree of selectivity (bronchial *vs.* cardiac activity) *in vitro* as well as *in vivo*.[14–16]

Of the compounds tested, the most potent bronchodilator was VIIIn—A (BD-40-A) which was 10 times as potent as isoproterenol in affinity to isolated trachea of guinea-pig and 43 times as potent as salbutamol when given orally in guinea-pigs.[15] In *in vitro*, BD-40-A was 2–6 times more selective than salbutamol.[15] The duration of activity of BD-40-A was over 8 hr in anesthetized dog.[16] BD-40-A is being studied more extensively.

Experimental[17]

4′-Benzyloxy-3′-nitro-2-bromoacetophenone (II)——To a solution of 4′-benzyloxy-3′-nitroacetophenone (I)[4] (5.4 g) in $CHCl_3$ (60 ml) was added, dropwise, bromine (3.2 g). The reaction mixture was stirred at room temperature until Br_2 color had disappeared, and the solvent was evaporated under reduced pressure to give yellow crystals. The crystals were recrystallized from $CHCl_3$–*n*-hexane. mp 137°. Yield, 5.9 g (85%). *Anal.* Calcd. for $C_{15}H_{12}O_4NBr$: C, 51.45; H, 3.45; N, 4.00; Br, 22.82. Found: C, 51.30; H, 3.53; N, 4.32; Br, 23.05.

General Procedure for Preparation of 4′-Benzyloxy-3′-nitro-2-substituted Aminoacetophenones (IIIa—h) A solution of II (0.02 mole) and N-substituted amine (0.04 mole) in methyl ethyl ketone (60 ml) was refluxed for 1—3 hr. The reaction mixture was cooled to 5—10° and the precipitated N-substituted amine hydrobromide was filtered off. The filtrate was evaporated under reduced pressure and the residue was recrystallized from ethanol.

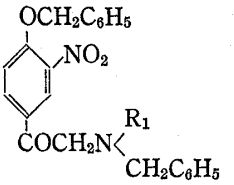
General Procedure for Preparation of 4-Benzyloxy-3-nitro-α-(N-substituted aminomethyl)benzyl Alcohols (IVa—h)——A mixture of (III) (0.01 mole) and $NaBH_4$ (0.01 mole) in EtOH (50 ml) (or a mixture of EtOH (35 ml)–$CHCl_3$ (15 ml) was stirred overnight at 15—25°, and to the reaction mixture was added water (5 ml). The mixture was evaporated under reduced pressure and the residue was extracted with benzene. The extract, after being washed with H_2O and dried over $MgSO_4$, was evaporated to give IV quantitatively. IVb—h were noncrystalline products, which were used without further purification in the subsequent step. Identification was based on absence of IR absorption in the region of the precursor ketone (1685—1695 cm^{-1}) and observation of a single spot on silica gel TLC plates using benzene–ethyl acetate (5: 1) as the solvent system.

4-Benzyloxy-3-nitro-α-(N-benzyl-N-isopropylaminomethyl)benzyl Alcohol (IVa)——mp 97° (EtOH). Yield, 91%. *Anal.* Calcd. for $C_{25}H_{28}O_4N_2$: C, 71.41; H, 6.71; N, 6.66. Found: C, 71.55; H, 6.88; N, 6.71. NMR ($CDCl_3$) δ: 1.00, 1.17 (each 3H, both d, $-CH(C\underline{H}_3)_2$), 2.49 (2H, m, $-CH(OH)\ C\underline{H}_2-$), 2.99 (1H, m, $-C\underline{H}-(CH_3)_2$), 3.50, 3.75, (2H, AB-q, $>NC\underline{H}_2C_6H_5$), 4.38 (1H, dd, $-C\underline{H}(OH)-$), 5.15 (2H, s, $-C\underline{H}_2C_6H_5$), 7.01—7.78 (13H, m, aromatic protons).

4-Benzyloxy-3-nitro-α-(N-benzyl-N-(α,α-dimethylphenethyl)aminomethyl)benzyl Alcohol (IVh)——mp 104° (MeOH). Yield, 96%. *Anal.* Calcd. for $C_{32}H_{34}O_4N_2$: C, 75.27; H, 6.71; N, 5.49. Found: C, 75.12; H, 6.59; N, 5.64. NMR $CDCl_3$) δ: 1.23 (6H, s, 2-CH_3), 2.87 (2H, d, $-CH(OH)C\underline{H}_2-$), 2.88 (2H, s, $-C(CH_3)_2C\underline{H}_2-$), 3.79, 4.18 (2H, AB-q, $>NC\underline{H}_2C_6H_5$), 4.04 (1H, t, $-C\underline{H}(OH)-$) 5.24 (2H, s, $-OC\underline{H}_2C_6H_5$), 7.04—7.64 (18H, m, aromatic protons).

14) H. Ida, *Arzneimittels-Forsch.*, **26**, 839 (1976).
15) H. Ida, *Arzneimittels-Forsch.*, **26**, 1337 (1976).
16) H. Ida, *Jpn. J. Pharmacol.*, **26**, 166P (1976).
17) All melting points were uncorrected. NMR spectra were recorded with JEOL MH-100 spectrometer (100 MHz) by using $(CH_3)_4Si$ as internal standard. The following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, dd=double doublet. Silica gel D-5 (Camag) and 60 F_{254} (Merck) were used for TLC. For column chromatography, silica gel (<100 mesh, Kanto Chemical Co., Inc.) was used.

Table III. 4′-Benzyloxy-3′-nitro-2-substituted Aminoacetophenones



Compd. No.	R_1	mp (°C)	Yield (%)	Formula	Analysis % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
IIIa	$CH(CH_3)_2$	93	85	$C_{25}H_{26}O_4N_2$	71.75	6.26	6.69	71.48	6.48	6.70
IIIb	$C(CH_3)_3$	103	78	$C_{26}H_{28}O_4N_2$	72.20	6.52	6.48	72.00	6.62	6.41
IIIc	$CH(CH_3)CH_2C_6H_4CH_3$-(*p*)	95	86	$C_{32}H_{32}O_4N_2$	75.57	6.34	5.51	75.32	6.07	5.60
IIId	$CH(CH_3)CH_2C_6H_4OH$-(*p*)	85	85	$C_{31}H_{30}O_5N_2$	72.92	5.92	5.49	72.66	6.08	5.66
IIIe	$CH(CH_3)CH_2C_6H_4OCH_3$-(*p*)	102	86	$C_{32}H_{32}O_5N_2$	73.26	6.15	5.34	72.68	6.19	5.42
IIIf	$CH(CH_3)CH_2CH_2C_6H_4OH$-(*p*)	*a*)	—							
IIIg	$CH(CH_3)CH_2CH_2$-c-C_6H_{11}	*b*)	81							
IIIh	$C(CH_3)_2CH_2C_6H_5$	143	65	$C_{32}H_{32}O_4N_2$	75.57	6.34	5.51	75.65	6.34	5.61

a) used for subsequent reaction without purification

b) amorphous solid, purified by chromatography on silica gel using benzene as eluent
NMR ($CDCl_3$) δ: 1.02 (3H, d, $-CH_3$), 0.80—1.70 (15H, m, $-CH_2CH_2C_6H_{11}$), 2.56 (1H, m, $>CHCH_3$), 3.31, 3.67 and 3.50, 3.71 (each 2H, both ABq, $>NCH_2C_6H_5$, $-COCH_2-$), 5.16 (2H, s, $-OCH_2C_6H_5$), 6.91 (1H, d, 2′-H), 7.10—7.40 (10H, m, 2-C_6H_5), 7.81 (1H, dd, 6′-H), 8.35 (1H, d, 5′-H)

Separation of 4-Benzyloxy-3-nitro-α-[N-benzyl-N-(3-cyclohexyl-1-methylpropyl)aminomethyl]benzyl Alcohol (IVg) into IVg-A and IVg-B——IVg, a gum (1 g), obtained by general procedure was chromatographed on 50 g of silica gel using benzene as the eluent to give 0.45 g of IVg-A, mp 71°, as the first fraction, 0.4 g of a mixture of IVg-A and IVg-B as the second fraction, and 0.1 g of IVg-B, a gum, as the third fraction. IVg-A. *Anal.* Calcd. for $C_{32}H_{40}O_4N_2$: C, 74.39; H, 7.80; N, 5.42. Found: C, 74.52; H, 7.98; N, 5.74. NMR ($CDCl_3$) δ: 0.97 (3H, d, $>CHCH_3$), 0.90—1.80 (15H, m, $-CH_2CH_2C_6H_{11}$), 2.47 (2H, m, $-CH(OH)CH_2-$), 3.42, 3.78 (2H, AB-q, $>NCH_2C_6H_5$), 4.46 (1H, dd, $-CH(OH)-$), 5.11 (2H, s, $-OCH_2C_6H_5$), 6.95—7.72 (13H, m, aromatic protons). IVg-B, NMR ($CDCl_3$) δ: 1.02 (3H, d, $>CHCH_3$), 0.90—1.80 (15H, m, $-CH_2CH_2C_6H_{11}$), 2.53 (2H, m, $-CH(OH)CH_2-$), 3.61 (2H, s, $>NCH_2C_6H_5$), 4.25 (1H, dd, $>CHOH$), 5.11 (2H, s, $-OCH_2C_6H_5$), 6.90—7.80 (13H, m, aromatic protons).

General Procedure for Preparation of 3-Amino-4-benzyloxy-α-(N-substituted aminomethyl)benzyl Alcohols (Va—h)——To a mixture of IV (0.02 mole), 1N HCl (25 ml) and MeOH (75 ml) was added with stirring reduced iron powders (0.08 mole), and refluxed for 40 min. The resulting black precipitates were filtered off, to the filtrate was added 1N NaOH (20 ml) and the mixture was evaporated under reduced pressure. The residue was extracted with benzene and the extract, after being washed with water and dried over $MgSO_4$, was evaporated to give V in 80—90% yield. Vd—h were used for the subsequent reaction after purification by column chromatography on silica gel using benzene-ethyl acetate as the eluent. Identification was based on observation of a single spot different from one of a precursor nitro compound on silica gel TLC using benzene–ethyl acetate (4: 1) as the solvent system.

3-Amino-4-benzyloxy-α-(N-benzyl-N-isopropylaminomethyl)benzyl Alcohol (Va)——mp 77°. Yield, 89%: *Anal.* Calcd. for $C_{25}H_{30}O_2N_2$: C, 76.89; H, 7.74; N, 7.17. Found: C, 77.21; H, 8.08; N, 7.40. NMR ($CDCl_3$) δ: 1.00, 1.06 (each 3H, both d, 2-CH_3), 2.53 (2H, m, $-CH(OH)CH_2-$), 3.00 (1H, m, $-CH(CH_3)_2$), 3.52, 3.82 (2H, AB-q, $>NCH_2C_6H_5$), 4.45 (1H, dd, $-CH(OH)-$), 5.04 (2H, s, $-OCH_2C_6H_5$), 6.60 (1H, dd, 6-H), 6.71 (1H, d, 2-H), 6.79 (1H, d, 5-H), 7.20—7.50 (10H, m, $2\times C_6H_5$).

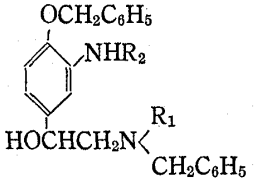
3-Amino-4-benzyloxy-α-(N-benzyl-N-*tert*-butylaminomethyl)benzyl Alcohol (Vb)——mp 67°. Yield, 90%. *Anal.* Calcd. for $C_{26}H_{32}O_2N_2$: C, 77.19; H, 7.97; N, 6.92. Found: C, 77.10; H, 8.26; N, 6.94. NMR ($CDCl_3$) δ: 1.17 (9H, s, 3-CH_3), 2.64 (2H, m, $-CH(OH)CH_2-$), 3.55, 3.95 (2H, AB-q, $>NCH_2C_6H_5$), 3.93 (1H, dd, $-CH(OH)-$), 5.00 (2H, s, $-OCH_2C_6H_5$), 6.47 (1H, dd, 6-H), 6.52 (1H, d, 2-H), 6.73 (1H, d, 5-H), 7.10—7.50 (10H, m, $2\times C_6H_5$).

Separation of 3-Amino-4-benzyloxy-α-[N-benzyl-N-(α-methyl-*p*-methylphenethyl)aminomethyl]benzyl Alcohol (Vc) into Vc-A and Vc-B——Vc, a brown gum (4.7 g), obtained by general procedure was dissolved in a mixture of *n*-hexane–benzene (3: 1) and allowed to stand for 2 days at room temperature. The solid which separated was collected by filtration and the filtrate was retained for further examination. The solid was recrystallized from benzene–*n*-hexane to give Vc-A (2.3 g), mp 117°. *Anal.* Calcd. for $C_{32}H_{36}O_2N_2$: C, 79.96; H, 7.55; N, 5.83. Found: C, 80.14; H, 7.85; N, 5.96. NMR ($CDCl_3$) δ:0.98 (3H, d, $>CH(CH_3)$)

2.28 (3H, s, $-CH_3$), 3.46, 3.86 (2H, AB-q, $>NC\underline{H}_2C_6H_5$, $J=13$ Hz), 4.42 (1H, dd, $-C\underline{H}OH-$), 5.00 (2H, s, $-OC\underline{H}_2C_6H_5$), 6.50—7.50 (17H, m, aromatic protons). The filtrate retained in the above experiment was evaporated under reduced pressure, and the residue was chromatographed on silica gel (40 g) using benzene–ethyl acetate (3: 1) as the eluent to give 1.9 g, a gum, of Vc-B. NMR ($CDCl_3$) δ: 1.02 (3H, d, $>CHC\underline{H}_3$), 2.28 (3H, s, $-CH_3$), 3.69, 3.86 (2H, AB-q, $>NC\underline{H}_2C_6H_5$, $J=14$ Hz), 4.33 (1H, dd, $>C\underline{H}OH$), 5.03 (2H, s, $-OC\underline{H}_2-C_6H_5$), 6.50—7.50 (17H, m, aromatic protons).

General Procedure for Preparation of 4-Benzyloxy-3-acylamino-α-[N-substituted aminomethyl]benzyl Alcohols (VIa-r) Method A. (Formylation)——To a solution of V (0.01 mole) in $CHCl_3$ (10 ml) was added a mixture of HCOOH–Ac_2O (3: 5 v/v, 4 ml), and stirred for 2 hr at 15—25°. The reaction mixture was evaporated under reduced pressure at 40—50°, and the residue was dissolved in methanol (100 ml). To the methanol

TABLE IV. 3-Acylamino-4-benzyloxy-α-(N-benzyl-N-substituted aminomethyl) benzyl Alcohols



Compd. No.	R_1	R_2	mp (°C)	Recrystn. solvent	Formula	Analysis (%) Calcd. (Found) C	H	N
VIa	$CH(CH_3)_2$	CHO	*a*)				*b*)	
VIb	$CH(CH_3)_2$	$COCH_3$	*a*)				*b*)	
VIc	$CH(CH_3)_2$	$COCH_2OCH_2C_6H_5$	95	iso-PrOH	$C_{34}H_{38}O_4N_2$	75.81 (75.49)	7.11 (7.12)	5.20 (5.34)
VId	$C(CH_3)_3$	CHO	*a*)				*b*)	
VIe	$C(CH_3)_3$	$COCH_2NHCHO$	148	iso-PrOH	$C_{29}H_{35}O_4N_3$	71.14 (71.22)	7.21 (7.06)	8.58 (8.58)
VIf	$C(CH_3)_3$	$COCH_2NHCOCH_3$	149	iso-PrOH	$C_{30}H_{37}O_4N_3$	71.54 (71.89)	7.41 (7.62)	8.34 (8.07)
VIg	$C(CH_3)_3$	$COCH_2CH_2NHCHO$	135	iso-PrOH	$C_{30}H_{37}O_4N_3$	71.54 (71.35)	7.41 (7.38)	8.34 (8.31)
VIh	$C(CH_3)_3$	$COCH_2CH_2OCH_2C_6H_5$	91	iso-PrOH	$C_{36}H_{42}O_4N_2$	76.29 (76.22)	7.47 (7.48)	4.94 (5.08)
VIi	$C(CH_3)_3$	$CO(CH_2)_3NHCHO$	*a*)				*c*)	
VIj	$C(CH_3)_3$	COC_6H_4OH-(*p*)	150 (HCl)	EtOH–ether	$C_{33}H_{36}O_4N_2\cdot HCl$	70.64 (70.57)	6.65 (6.61)	4.99 (4.83)
VIk	$C(CH_3)_3$	COC_6H_5OH-(m)	*a*)				*c*)	
VIl A	$CH(CH_3)CH_2C_6H_4CH_3$-(*p*)	CHO	127	benzene–*n*-hexane	$C_{33}H_{36}O_3N_2$	77.92 (78.03)	7.13 (7.24)	5.51 (5.42)
VIl B	$CH(CH_3)CH_2C_6H_4CH_3$-(*p*)	CHO	*a*)					
VIm A *d*)	$CH(CH_3)CH_2C_6H_4OH$-(*p*)	CHO	137	EtOAc–C_6H_6	$C_{32}H_{34}O_4N_2$	75.27 (75.53)	6.71 (6.90)	5.49 (5.47)
VIm B	$CH(CH_3)CH_2C_6H_4OH$-(*p*)	CHO	*a*)					
VIn A *d*)	$CH(CH_3)CH_2C_6H_4OCH_3$-(*p*)	CHO	114	iso-PrOH	$C_{33}H_{36}O_4N_2$	75.54 (75.51)	6.92 (7.04)	5.34 (5.42)
VIn B	$CH(CH_3)CH_2C_6H_4OCH_3$-(*p*)	CHO	*a*)					
Vo	$CH(CH_3)CH_2CH_2C_6H_4OH$-(*p*)	CHO	146	MeOH	$C_{33}H_{36}O_4N_2$	75.54 (75.25)	6.92 (6.98)	5.34 (5.37)
Vp	$CH(CH_3)CH_2CH_2$-c-C_6H_{11}	CHO	*a*)				*b*)	
Vq	$C(CH_3)_2CH_2C_6H_5$	CHO	158	benzene–*n*-hexane	$C_{33}H_{36}O_3N_2$	77.92 (78.03)	7.13 (7.24)	5.51 (5.42)
Vr	$CH(CH_3)CH_2C_6H_4OH$-(*p*)	$COCH_2NHCOCH_3$	226	iso-PrOH			*b*)	

a) amorphous glass
b) Compound was not analyzed but hydrogenated without further purification.
c) purified by column chromatgraphy on silica gel using benzene–ethyl acetate as eluent
d) The separation of isomer A and B was made and identified by NMR (see experimental part).

solution was added K_2CO_3 (10 g), and the mixture was stirred during 2 hr at room temperature. The mixture was evaporated, and the residue was extracted with benzene. The extract, after being washed with water and dried over $MgSO_4$, was evaporated to give N-formyl compounds VIa, VId, VIm—r quantitatively.

Method B——To a solution of Ve·HCl (4.4 g, 0.01 mole) and N-formylglycine (2.2 g, 0.02 mole) in 50 ml of pyridine was added dicyclohexylcarbodiimide (4.2 g, 0.02 mole) and stirred overnight. The deposited dicyclohexylurea was filtered off, and the filtrate was evaporated under reduced pressure. The residue was dissolved in 5% KOH–MeOH solution and warmed at 50—60° for 30 min. The reaction mixture was evaporated under reduced pressure, and the residue was extracted with benzene. The extract was washed with water, dried over $MgSO_4$ and evaporated to give a solid, which was recrystallized from isopropanol to give VIe in 75% yield. VIc, VIf—k and VIr were obtained by method B.

Separation of 4-Benzyloxy-3-formamido-α-[N-benzyl-N-(*p*-hydroxy-α-methylphenethyl)aminomethyl]-benzyl Alcohol (VIm) into VIm-A and VIm-B——VIn, a gum (2.4 g), was dissolved in benzene (30 ml) and allowed to stand for 3 days. The solid which separated was collected by filtration and the filtrate was retained for further examination. The solid was recrystallized from benzene–ethyl acetate (3: 1) to give 1.2 g of VIm-A, mp 135—137°. NMR ($CDCl_3$) δ: 0.97 (3H, d, $-CH_3$), 2.35—2.80 (4H, m, $-CH(OH)C\underline{H}_2-$, $-C\underline{H}_2C_6H_4OH(p)$), 3.10 (1H, m, $>C\underline{H}CH_3$), 3.47, 3.87 (2H, AB-q, $>NC\underline{H}_2C_6H_5$), 4.50 (1H, m, $-C\underline{H}OH-$), 5.00 (2H, s, $-OC\underline{H}_2C_6H_5$). The filtrate retained in the above experiment was evaporated under reduced pressure, and the residue was chromatographed on silica gel (15 g) with benzene–ethyl acetate as the eluent to give Vn-B (1.0 g), a gum. Vm-B ($CDCl_3$) δ: 1.00 (3H, d, $-CH_3$), 2.2—3.10 (5H, $-C\underline{H}_2C_6H_4OH(p)$, $-CH(OH)C\underline{H}_2-$, $>NC\underline{H}(CH_3)-$), 3.69 (2H, s, $-NC\underline{H}_2C_6H_5$), 4.29 (1H, m, $-C\underline{H}(OH)-$), 5.00 (2H, s, $-OC\underline{H}_2C_6H_5$).

Separation of 4-Benzyloxy-3-formamido-α-[N-benzyl-N-(*p*-methoxy-α-methylphenethyl)aminomethyl]-benzyl Alcohol (VIn) into VIn-A and VIn-B——A solution of VIn (5.1 g), a gum, obtained by general procedure and fumaric acid (1.1 g) in methanol 20 ml was evaporated under reduced pressure. The residue was dissolved in ethyl acetate (80 ml) and allowed to stand for 2 days. The solid which separated was collected by filtration and the filtrate was retained for further examination. The solid was recrystallized from isopropanol (50 ml) to give Vin-A·fumarate (3.2 g), mp 173°. VIn-A·fumarate (3.2 g) was treated with 2.5% KOH–MeOH (25 ml), and the mixture, after being added H_2O (50 ml), was extracted with toluene. The extract was washed with water, dried over $MgSO_4$, and evaporated under reduced pressure to give VIn-A (2.6 g). mp 114° (iso-PrOH). NMR ($CDCl_3$) δ: 0.97 (3H, d, $>CHC\underline{H}_3$), 2.40—2.90 (4H, m, $-CHOHC\underline{H}_2-$, $-C\underline{H}_2C_6H_4OCH_3(p)$), 3.10 (1H, m, $>NC\underline{H}(CH_3)-$), 3.46, 3.86 (2H, AB-q, $>NC\underline{H}_2C_6H_5$), 3.73 (3H, s, $-OCH_3$), 4.51 (1H, m, $-C\underline{H}OH-$), 5.02 (2H, s, $-C\underline{H}_2C_6H_5$). The filtrate retained in the above experiment was evaporated under reduced pressure. The residue was treated with 2.5% KOH–methanolic solution to give crude VIn-B, which was chromatographed over silica gel (20 g) with benzene–ethyl acetate (4: 1) as the eluent to give VIn-B (1.8 g), a gum. NMR ($CDCl_3$) δ: 1.00 (3H, d, $>CHC\underline{H}_3$), 2.20—3.10 (5H, m, $-CH(OH)CH_2-$, $>NC\underline{H}(CH_3)$, $-C\underline{H}_2C_6H_4OCH_3(p)$), 3.72 (3H, s, $-OCH_3$), 3.72 (2H, s, $>NC\underline{H}_2C_6H_5$), 4.40 (1H, m, $-C\underline{H}OH-$), 5.01 (2H, s, $-OC\underline{H}_2C_6H_5$).

General Procedure for Preparation of 3-Acylamino-4-hydroxy-α-(N-substituted aminomethyl)benzyl Alcohols (VIII)——A mixture of VI (0.02 mole), 100 ml of isopropanol (or ethanol) and 10% Pd/C (1 g) was hydrogenated at room temperature until H_2 uptake had ceased. The reaction mixture was filtered, and the filtrate was evaporated under reduced pressure to give an amorphous solid of crude VIII. The crude VIII was converted into the crystalline salt.

3-Benzyloxy-5-nitrobenzoic Acid (IX)——A mixture of methyl 3-hydroxy-5-nitrobenzoate (20 g)[18] and benzyl chloride (1.3 g) in a solution of sodium (2.3 g) in methanol (200 ml) was refluxed for 15 hr. The precipitated sodium chloride was filtered off, and the filtrate was cooled to give yellow crystals (23 g, mp 67°) of methyl 3-benzyloxy-5-nitrobenzoate. A mixture of methyl 3-benzyloxy-5-nitrobenzoate (15 g), KOH (10 g) and 80% EtOH (150 ml) was refluxed for 3 hr. A reaction mixture was acidified with 10% HCl. The deposited crystals were collected and recrystallized from 50% EtOH to give IX (12.5 g), mp 165—166°. *Anal.* Calcd. for $C_{14}H_{11}O_5N$: C, 61.54; H, 4.06; N, 5.13. Found: C, 61.51; H, 4.13; N, 5.09.

3′-Benzyloxy-5′-nitro-2-bromoacetophenone (X)——X was prepared from IX *via* 3′-benzyloxy-5′-nitro-2-diazoacetophenone.[19] mp 89—90° (from ether–*n*-hexane). Yield, 75%. *Anal.* Calcd. for $C_{15}H_{12}O_4NBr$: C, 51.45; H, 3.45; N, 4.00; Br, 22.82. Found: C, 51.49; H, 3.61; N, 4.07; Br, 23.19.

3′-Benzyloxy-5′-nitro-2-(N-benzyl-N-*tert*-butylamino)acetophenone (XI)——A mixture of X (3.5 g) and N-benzyl-N-*tert*-butylamine (3.3 g) in 30 ml of methyl ethyl ketone was refluxed for 2 hr. After cooling, the deposited N-benzyl-N-*tert*-butylamine hydrobromide was filtered off. The filtrate was evaporated under reduced pressure and the residue was chromatographed on silica gel (50 g) using benzene as the eluent to give XI (3.5 g), a gum. NMR ($CDCl_3$) δ: 1.24 (9H, s, $-C(CH_3)_3$), 3.75, 3.86 (each 2H, both s, $-COC\underline{H}_2NC\underline{H}_2-C_6H_5$), 5.03 (2H, s, $-OC\underline{H}_2C_6H_5$), 6.90—8.40 (13H, m, aromatic protons).

3-Benzyloxy-5-nitro-α-(N-benzyl-N-*tert*-butylaminomethyl)benzyl Alcohol (XII)——A mixture of XI (3.5 g), $NaBH_4$ (0.5 g), tetrahydrofuran (10 ml) and ethanol (20 ml) was stirred overnight at room tempera-

18) E. Epstein and M. Meyer, *J. Am. Chem. Soc.*, **77**, 4059 (1955).
19) H. King and T.S. Work, *J. Chem. Soc.*, **1940**, 1307.

ture. The reaction mixture was evaporated, and the residue was extracted with benzene. The extract was washed with water, dried over $MgSO_4$ and evaporated under reduced pressure to give a gum (3.3 g) of XII. NMR ($CDCl_3$) δ: 1.17 (9H, s, 3-CH_3), 2.63 (2H, m, -CH(OH)C$\underline{H}_2$-), 3.56, 3.91 (2H, AB-q, -NC$\underline{H}_2C_6H_5$), 5.00 (2H, s, -OC$\underline{H}_2C_6H_5$), 7.0—7.80 (13H, m, aromatic protons).

3,5-Bis(methoxycarboxamido)acetophenone (XIII)——To a solution of 3′,5′-diaminoacetophenone (1.5 g)[20] in pyridine (20 ml) was added methyl chloroformate (2.1 g) at 0—10°. The reaction mixture was stirred for 3 hr, and then poured into ice-water. The deposited crystals were collected and recrystallized from iso-PrOH to give XIII (1.6 g), mp 164—165°. *Anal.* Calcd. for $C_{12}H_{14}O_5N_2$: C, 54.13; H, 5.30; N, 10.52. Found: C, 54.01; H, 5.28; N, 10.36.

3′,5′-Bis(methoxycarboxamido)-2-bromoacetophenone (XIV)——To a solution of XIII (2.3 g) in $CHCl_3$ (250 ml), Br_2 (1.4 g) was added dropwise at room temperature. The reaction mixture was stirred until Br_2-color had disappeared. The crystals separated were collected by filtration and washed with $CHCl_3$ to give XIV (1.8 g), mp 199—200°. *Anal.* Calcd. for $C_{12}H_{13}O_5N_2Br$: C, 41.76; H, 3.80; N, 8.12. Found: C, 42.08; H, 3.74; N, 8.46.

3′,5′-Bis(methoxycarboxamido)-2-(N-Benzyl-N-*tert*-butylamino)acetophenone (XV)——A mixture of XIV (1.2 g) and N-benzyl-N-*tert*-butylamine (1.2 g) in methyl ethyl ketone (15 ml) was refluxed for 15 hr. The precipitates separated were filtered off, and the filtrate was evaporated under reduced pressure to give a solid. The solid was recrystallized from EtOH to give XV (0.7 g), mp 159—160°. *Anal.* Calcd. for $C_{23}H_{29}O_5N_3$: C, 64.62; H, 6.84; N, 9.83. Found: C, 64.40; H, 6.86; N, 9.48.

3′,5′-Diamino-2-(N-benzyl-N-*tert*-butylamino)acetophenone (XVI)——A solution of XV·HBr (3 g) in 48% HBr (30 ml) was heated at 120° for 2 hr. The reaction mixture was evaporated under reduced pressure at 60—80°. To the residue, Na_2CO_3 (10 g) and H_2O (20 ml) were added and extracted with ethyl acetate (50 ml). The extract was washed with water, dried over $MgSO_4$ and evaporated under reduced pressure to give XVI (1.7 g). NMR (d_6-DMSO) δ: 1.06 (9H, s, 3-CH_3), 3.78 (4H, s, -COC$\underline{H}_2$NC$\underline{H}_2$-), 4.80 (4H, broad s, 2-NH_2), 6.00 (1H, 4′-H), 6.28 (2H, d, 3′,5′-H), 7.10—7.50 (5H, m, -C_6H_5). IR ν_{max}^{KBr} cm^{-1}: 1690 (-$\overset{O}{\overset{\|}{C}}$-), 3360, 3450 ($NH_2$).

3-Amino-5-benzyloxy-α-(N-benzyl-N-*tert*-butylaminomethyl)benzyl Alcohol (XVIIa)——A solution of XII (1.5 g) in EtOH (30 ml) was hydrogenated in the presence of Raney-nickel (1 g) until H_2 (250 ml) had been absorbed. The mixture was filtered, and the filtrate was evaporated under reduced pressure. The residue was chromatographed on silica gel (20 g) using benzene as the eluent to give XVIIa (1 g), a yellow gum. NMR ($CDCl_3$) δ: 1.15 (9H, s, 3-CH_3), 2.63 (2H, m, -CH(OH)C$\underline{H}_2$-), 3.54, 3.93 (2H, AB-q, >NC$\underline{H}_2C_6H_5$), 4.91 (2H, s, -OC$\underline{H}_2C_6H_5$), 6.04—6.24 (3H, m, 2,4,6-H), 7.10—7.50 (10H, m, 2-C_6H_5).

3-Formamido-5-hydroxy-α-(N-*tert*-butylaminomethyl)benzyl Alcohol·1/2 fumarate (XIXa)——3-Benzyloxy-5-formamido-α-(N-benzyl-N-*tert*-butylaminomethyl)benzyl alcohol (XVIIIa) (0.7 g) was obtained from XVIIa (0.8 g) by the procedure described for preparation of VI (method A). XVIIIa was used for the next reaction without purification. A solution of XVIIIa (0.7 g) in EtOH (10 ml) was hydrogenated in the presence of 10% Pd-C (0.3 g) at atmospheric pressure until the uptake of hydrogen had ceased. The mixture was filtered, the filtrate was evaporated under reduced pressure to give an amorphous solid. A solution of the amorphous solid (0.25 g) and fumaric acid (0.06 g) in EtOH (5 ml) was allowed to stand overnight to give white crystals of XIXa (0.28 g), mp 254°. *Anal.* Calcd. for $C_{15}H_{22}O_5N_2$: C, 58.05; H, 7.15; N, 9.03. Found: C, 57.85; H, 7.22; N, 8.75.

3,5-Bis(formamido)-α-(N-*tert*-butylaminomethyl)benzyl Alcohol (XIXb)——3,5-Bis(formamido)-α-(N-benzyl-N-*tert*-butylaminomethyl)benzyl alcohol (XVIIIb) (0.9 g) was obtained *via* XVIIb from XVI (1.1 g) by the procedure described for preparation of VI. XVIIIb was used for the next reaction without purification. A solution of XVIIIb (0.9 g) in EtOH (20 ml) was hydrogenated in the presence of 10% Pd-C (0.2 g) at room temperature until H_2-uptake had ceased. The catalyst was filtered off, the filtrate was concentrated under reduced pressure to a volume of 15 ml. To the solution was added fumaric acid (0.14 g), dissolved and allowed to stand overnight to give white crystals of XIXb (0.62 g). mp 227—229°. *Anal.* Calcd. for $C_{16}H_{23}O_5N_3$: C, 56.96; H, 6.86; N, 12.45. Found: C, 57.25; H, 7.07; N, 12.17.

3,5-Bis(methoxycarboxamido)-α-(N-*tert*-butylaminomethyl)benzyl Alcohol Hydrochloride (XX)——A solution of XV·HCl (0.35 g) in EtOH (20 ml) was hydrogenated in the presence of 10% Pd-C (0.1 g) at room temperature until H_2-uptake had ceased. The mixture was filtered and the filtrate was evaporated under reduced pressure to give a solid, which was recrystallized from EtOH–*n*-hexane to yield white crystals (0.17 g). mp 151—152°. *Anal.* Calcd. for $C_{16}H_{25}O_5N_3$·HCl·EtOH: C, 51.24; H, 7.64; N, 9.96. Found: C, 50.95; H, 7.54; N, 9.68.

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20) L. Berend and F. Heymann, *J. Prakt. Chem.*, **173**, 290 (1902).