d) Effect of a Substituent on a Phenyl Ring at the 1-Position of the Pyrazole—— Among the 4-nitroso-3,5-dimethylpyrazoles, 1-(*p*-chlorophenyl)- and 1-*p*-tolyl derivatives were most antifungal,[1] but in the series of 4-thiocyanato-3,5-dimethylpyrazoles, 1-(*m*-nitrophenyl)derivative was most effective. Substituents on the phenyl ring at the 1-position of 3-methyl-4-thiocyanato-1,5-diphenylpyrazole, however, did not exert remarkable effects on the antifungal activity.

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Thanks are also due to Mr. M. Kan for elemental analyses and to Mr. H. Nakamachi and Miss T. Hiratsuka for optical measurements.

Summary

4-Alkoxythiocarbonylthio- and 4-(N,N-disubstituted thiocarbamoylthio)pyrazoles and two thiocyanatopyrazoles were synthesized.

Antifungal activities of these compounds as well as those described in the preceding paper were tested.

In conclusion, 4-thiocyanatopyrazoles showed high antifungal activities of which 1-(*m*-nitrophenyl)-4-thiocyanato-3,5-dimethylpyrazole was most effective.

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26. Tadashi Sasaki, Ken Kanematsu, Katsumaro Minamoto,[*1] and Hajime Fujimura[*2] : Researches on Morphine-like Analgesics. I. Syntheses and Analgesic Activity of Desylamine Derivatives.

(*Department of Pharmacy, Tokyo College of Science,*[*1] *and Institute of Chemical Research, Kyoto University*[*2])

For the purpose of elucidating the relationship between effective partial structure of morphine skeleton (I′) and analgesic action, several compounds possessing the A-C rings in the morphine skeleton as the basic structure were synthesized. This papar is concerned with the synthesis of 2-dialkylamino-2-phenylacetophenone, the Mannich reaction of deoxybenzoin and the behavior of its product in the succeeding reaction.

The original report by Dodds, *et al.*[1] that diphenylethylamines and in particular 2-amino-1,2-diphenylethanol relieved pain associated with carcinoma in human subjects appears to have been a specialized circumstance.

Later they reported the failure to detect the production of analgesia by these compounds in rats. In 1960, (−)N,N-dimethyl-1,2-diphenylethylamine derived from (−)1,2-diphenylethylamine was found to be 0.33~0.5 times as potent as (−)morphine by Fujimura, *et al.*, whereas the (+)enantiomorph shows almost no activity.[2] Recently,

*1 Funagawara-machi, Sinjuku-ku, Tokyo (佐々木 正, 兼松 顕, 源 勝麿).

*2 Kosobe, Takatsuki, Osaka-fu (藤村 一).

1) E.C. Dodds, *et al.* : J. Physiol., **104**, 47 (1945); Nature **151**, 614 (1943). C.M. Suter : "Medicinal, Chemistry" Vol. **1**, 399 (1951).

2) K. Ogiu, H. Fujimura, Y. Yamakawa : Yakugaku Zasshi, **80**, 283 (1960).

Nakazaki[3] showed that the analgesically active (−)N,N-dimethyl-1,2-diphenylethylamine (IIa) had the (R)-configuration, which indicated the close stereochemical resemblance to (−)morphine. Since the A and C rings of morphine are almost perpendicular to each other, IIa might be expected to take an analogous conformation in approaching some reactive surface in the nervous system.

Now, considering hypothetical arrangement of morphine-like analgesic drug molecule at receptor surface, which was proposed by Beckett,[4] we took up the compounds of general formula (III). This idea might be taken to imply electrostatic forces (involving partial units of charge) between the oxygen and the biological structure concerned.

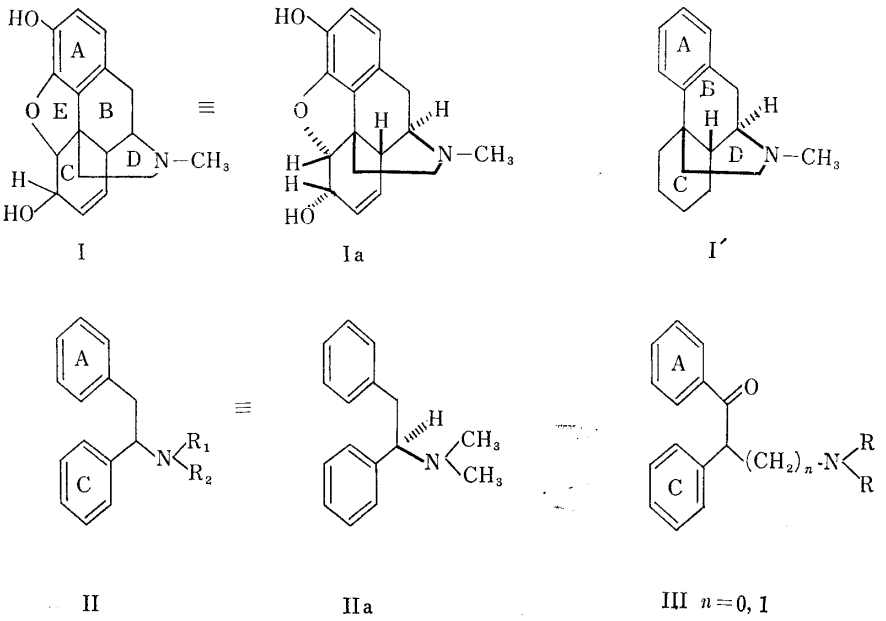


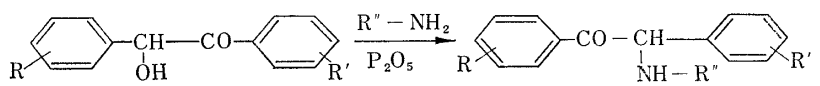
Chart 1.

The reaction which took place between benzoin and aliphatic or aromatic amines in the presence of phosphorus pentoxide was commonly known as the Voigt reaction.[5] However, the yield of the reaction of benzoin and secondary amines was not satisfactory in Voigt reaction. Therefore, 2-dimethylamino(piperidino, morpholino, pyrrolidino, phenethylamino)-2-phenylacetophenone was obtained in a good yield by reacting desyl chloride[6] with dimethylamine(piperidine, morpholine, pyrrolidine, phenethylamine) in a sealed tube.

For the structural proof of the base (IX) or (IX′) the infrared absorption spectrum was measured, which showing a strong absorption at 1670 cm^{-1} which could be assigned to the conjugated carbonyl group. This spectrum supports IX rather than IX′.

An attempt was made to reduce the carbonyl group of V by means of the Clemmensen reduction, which did not give the anticipated N,N-dimethyl-1,2-diphenylethylamine, but gave an unknown substance (X) of m.p. 124~125° as colorless needles in good yield, which was assumed to be *trans*-stilbene from its analytical values, and its infrared absorption spectrum which showed s sharp absorption at 1630, 1600, 1580, and

3) M. Nakazaki: Chem. & Ind. (London), **1962**, 1577; Bull. Chem. Soc. Japan, **36**, 161 (1963).
4) A.H. Beckett: Angew. Chem., **72**, 686 (1960).
5) K. Voigt: J. pract. Chem., **34**, 2 (1886).



6) A.H. Blatt "Org. Syntheses" Coll. Vol., **II**, 159 (1950).

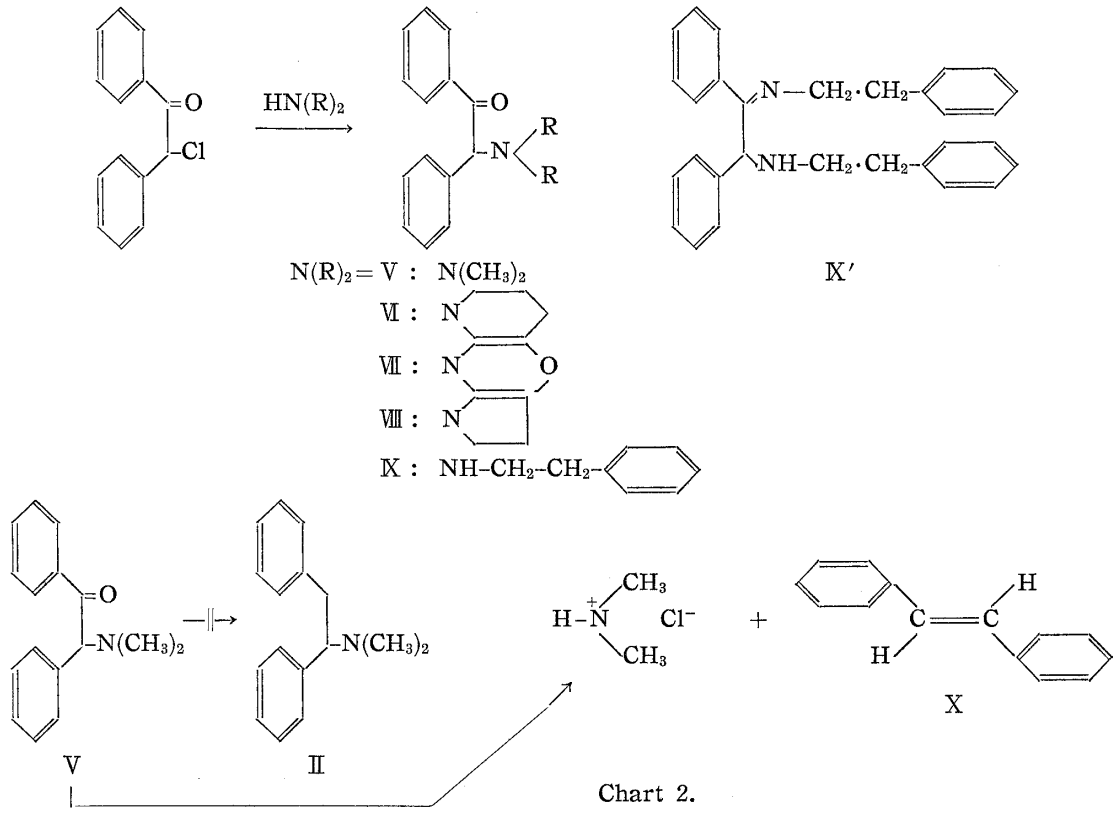


Chart 2.

1500 cm^{-1} owing to the presence of the double bond and a monosubstituted phenyl group, and also an absorption at 965 cm^{-1} which could be assigned to the C-H group.

Mannich bases (XII)~(XIV) were prepared by the condensation of deoxybenzoin (XI) with 30% formic acid or paraformaldehyde and secondary amine by warming in methanol. On the other hand, the reaction of XI and diethylamine under similar conditions gave an unknown substance (XV) of m.p. 108~109° as colorless plates instead of the expected Mannich base, which was assumed to be 4-oxo-2,4-diphenylbutyrophenone (XV) rather than methylenedeoxybenzoin (XVI)[7] from its infrared absorption spectrum, which was observed at 1690 cm^{-1} owing to the presence of the conjugated carbonyl group but did not show any absorption bands of terminal methylene group.

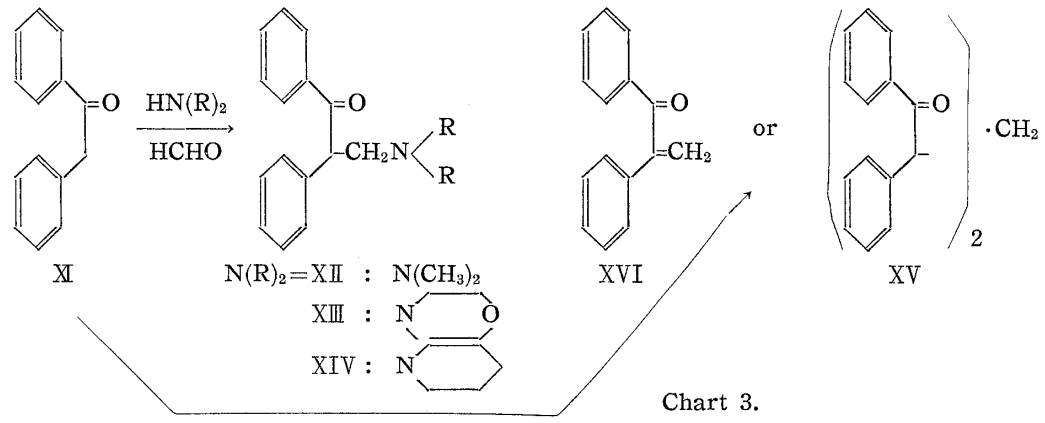


Chart 3.

Finally, the acute toxicity and analgesic action of the above-mentioned amines were examined with mice by modified Haffner's method.[8]

7) H. Fiesselmann, *et al.* : Chem. Ber., **89**, 27 (1956).
8) H. Fujimura, *et al.* : Bull. Inst. Chem. Research, Kyoto Univ., **25**, 36 (1951).

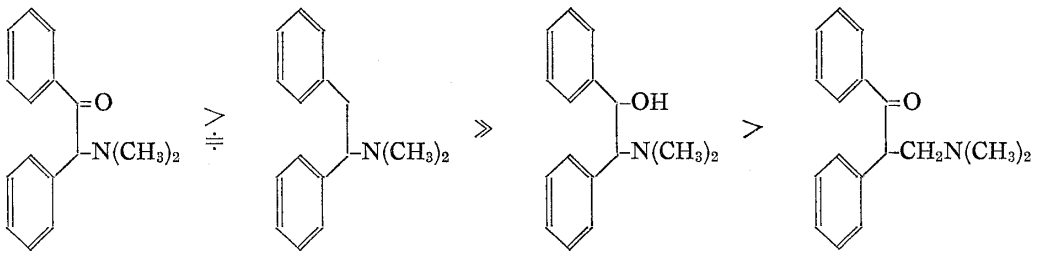
The values of LD_{50} and ED_{50} of these compounds were presented in Table I. In general formula (III), the derivatives of $n=0$ type generally produced a much stronger effect than those of $n=1$ type. V was almost the same as *l*-(−) (IIa) in its analgesic action, but more toxic. VI and IX were found to possess less toxic and more analgesic properties than *dl*-(±) (IIa). Moreover it was very interesting that the derivatives of $n=0$ type showed an increased solubility in water compared with diphenylethylamine derivatives. On the other hand, it was of considerable interest to note that many Mannich bases had little or no analgesic action, based on screening. A more detailed report will be presented elsewhere.

Table I. Acute Toxicity and Analgesic Activity in Mice

No.	LD_{50}[a] mg./10 g. s.c.	ED_{50}[a] mg./10 g. s.c.	LD_{50}/ED_{50}
V	1.12 (1.03～1.22)	0.16 (0.105～0.23)	7.0
VI	4.35 (3.75～5.05)	0.22 (0.138～0.352)	19.77
VII	ca. 8.0	0.5≒50%	
VIII	2.50 (2.23～2.80)	0.2≒40%	
IX	3.50 (3.24～3.79)	0.19 (0.144～0.251)	18.48
XII	4.0～5.0	0.4≒50%	
XIII	5.0～	0.2～0.4≒30%	
XIV	5.0～	0.3～0.5≒25%	
dl (IIa)	2.75 (2.41～3.06)	0.22 (0.119～0.407)	12.50
l (IIa)	2.71 (2.17～3.38)	0.14 (0.077～0.249)	19.35

a) Litchfield-Wilcoxon's method (p=0.05)

From these results and previous communications,[9] the relation between analgesic action and structure of diphenylethylamine type has been shown.



dl *dl, l* *erythro dl≒threo dl* *dl*

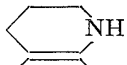
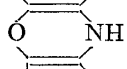
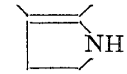
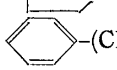
Experimental

Synthesis of 2-Dimethylamino(piperidino, morpholino, pyrrolidino, phenethylamino)-2-phenylacetophenone (V)～(IX)——To a solution of desyl chloride in a proper quantity of benzene or EtOH was added an excess dimethylamine (piperidine, morpholine, pyrrolidine, phenethylamine) in the corresponding solvent and the mixture was heated at 90～100° in a sealed tube for 4～5 hr. After cooling, the reaction mixture was basified with 10% NaOH and extracted with sufficient benzene. The benzene layer was dried over anhyd. Na_2SO_4, the solvent distilled off and the remaining oil, as an AcOEt solution, treated with dried HCl. Recrystallization of the precipitate from EtOH afforded in every case colorless prisms. Yield, 70～71% (Table II).

Clemmensen Reduction of V——To Zn-Hg prepared from 10 g. of Zn, 1 g. of $HgCl_2$, 0.5 ml. of conc. HCl and 15 ml. of H_2O was added 1 g. of V, 18 ml. of conc. HCl and 10 ml. of EtOH, and the mixture was heated on a water bath for 5 hr. After a while, long needles began to be precipitated. After the reaction was ended, the mixture was cooled and the resulting crystals were collected. Recrystallization from EtOH afforded X of m.p. 124～125°. Yield, 0.7 g. IR cm^{-1}: $\nu_{C=C}$ 1630, 1600, 1580

9) Y. Yamakawa: Yakugaku Zasshi, **80**, 295 (1960).

Table II.

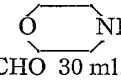
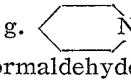
Compd. No.	Reactants (g.)	Yield (g.)	m.p. (°C)	Formula	Analysis (%) Calcd. C	Calcd. H	Found C	Found H
V	IV 2, $(CH_3)NH$ 1.3	1.7	232~234 (dec.)	$C_{16}H_{17}ON \cdot HCl \cdot \frac{1}{2}H_2O$	67.42	6.67	67.48	7.01
VI	IV 2,  NH 2.6	2.0	219~221 (dec.)	$C_{19}H_{21}ON \cdot HCl \cdot \frac{1}{2}H_2O$	70.26	7.08	70.21	7.31
VII	IV 2,  NH 1.7	2.3	199~201	$C_{18}H_{19}O_2N \cdot HCl \cdot \frac{1}{2}H_2O$	65.09	6.43	65.97	6.69
VIII	IV 7,  NH 4.3	6.5	235~238	$C_{18}H_{17}ON \cdot HCl$	71.63	6.68	71.83	6.60
IX	IV 4.5,  $-(CH_2)_2-NH_2$ 4.7	4.9	198~200	$C_{21}H_{21}ON \cdot HCl$	75.09	6.30	75.03	6.05

($CHCl_3$); δ_{C-H} 965($CHCl_3$). Each absorption is in a complete accordance with that of an authentic sample. *Anal.* Calcd. for $C_{13}H_{12}$: C, 93.29; H, 6.71. Found : C, 93.26; H, 7.03. Furthermore, dimethylamine was separated as picrate from the above filtrate.

Mannich Reaction of Deoxybenzoin (XI)——1) This series of compounds were prepared according to the usual method, in which the employed amount of each reagent, yields are summarized below. To an alcoholic solution of XI was added secondary amines (30% aq. dimethylamine, morpholine, piperidine), several drops of conc. HCl and 30% aq. HCHO (or paraformaldehyde). After reflux for 2 hr. on a water bath, the reaction mixture was basified with 20% NaOH and extracted with $CHCl_3$. The $CHCl_3$ extract was combined, dried over anhyd. Na_2SO_4 and the solvent was evaporated. Repeated recrystallization of the residue from AcOEt gave substances described in the Table III.

2) 2 g. of XI, 10 ml. of EtOH, 0.5 g. of diethylamine, 3 ml. of 30% HCHO and 3 drops of conc. HCl were combined and heated to reflux for 2 hr. The mixture was condensed *in vacuo*, basified with 20% NaOH and extracted with Et_2O. The combined ethereal layer was dried over anhyd. Na_2SO_4 and the Et_2O was evaporated. The vacuum distillation of the residue yielded a homogeneous oil of $b.p_{14}$ 135~145°, which solidified after standing overnight in a refrigerater. Recrystallization from Et_2O gave colorless leaflets of m.p. 108~109°. Qualitative test of N : (−). *Anal.* Calcd. for $C_{29}H_{24}O_2$: C, 86.14; H, 5.94. Found : C, 86.47; H, 5.92. IR cm^{-1} : $\nu_{C=O}$ 1690 ($CHCl_3$).

Table III.

Compd. No.	Reactants	Yield (g.)	m.p. (°C)	Formula	Analysis (%) Calcd. C	Calcd. H	Found C	Found H
XII	XI 2 g. 30% $(CH_3)_2NH$ 1 ml. 30% HCHO 3 ml.	2.0	165~168	$C_{17}H_{19}ON \cdot HCl \cdot \frac{1}{2}H_2O$	68.27	7.03	68.77	7.47
XIII	XI 2 g,  NH 0.9 ml. 30% HCHO 30 ml.	2.6	138~139	$C_{19}H_{21}O_2N$	77.26	7.17	77.18	7.28
XIV	XI 1.9 g.  NH·HCl 1.2 g. paraformaldehyde 0.8 g.	2.4	103~105	$C_{20}H_{23}ON$	82.86	7.90	82.15	8.16

The authors are deeply grateful to the members of Analytical Center of Kyoto University for elementary analysis.

Summary

1) 2-Dialkylamino-2-phenylacetophenone was prepared.

2) The Mannich reaction of deoxybenzoin was described.

3) The compounds of VI and IX were found to possess less toxic and more analgesic properties than (±)N,N-dimethyl-1,2-diphenylethylamine.

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