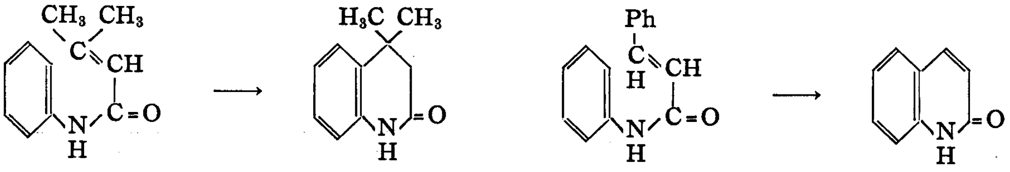
## Note

UDC 547.551.1'462.3.07

# **Tohru Hino and Takayuki Shioiri**: On the Reaction of N,N'-Dimethylfumaranilide with Aluminium Chloride.

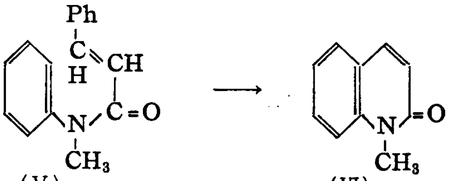
(*Faculty of Pharmaceutical Sciences, University of Tokyo*[*1])

It has been reported[1] that carbostyril derivatives (II and IV) were respectively obtained from 3-methylcrotonanilide and cinnamanilide when treated with aluminium chloride.

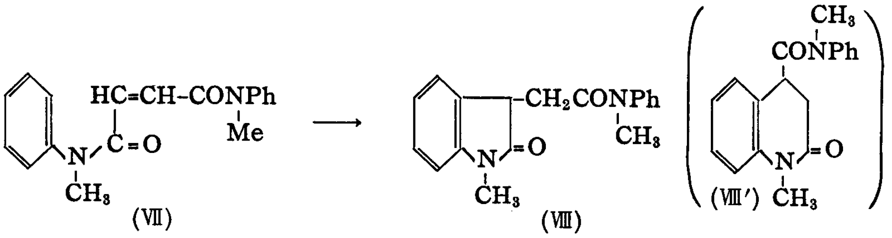


(I) (II) (III) (IV)

The reaction was now extented to N-methylcinnamanilide (V) and N,N'-dimethylfumaranilide (VII), when a carbostyril derivative (VI) was obtained from the former and the latter gave rise to a oxindole derivative (VIII).



(V) (VI)



(VII) (VIII)

Thus, (V) was heated with aluminium chloride at 100° and (VI) was obtained in 90% yield with liberation of a phenyl group. The structure of (VI) was confirmed by infrared spectrum and admixture with the authentic 1-methylcarbostyril. When (VII), prepared from fumaryl chloride and N-methylaniline by the Schotten-Baumann reaction, was heated with aluminium chloride at 180°, the starting material was recovered. However, under a more strenuous working condition, at 230~235°, with a large excess of aluminium chloride, this underwent cyclization to give (VIII) as pale yellow prisms in 57% yield; the compound (VIII') was not detected in the reaction product.

The infrared spectrum of (VIII) shows two amide CO bands at 1718 and 1660 $\text{cm}^{-1}$ in Nujol. The former is supposed to be due to C=O of oxindoles[2] which is fairly different from C=O of dihydrocarbostyril and the latter to C=O of anilide in the side chain. The ultraviolet spectral curve, $\lambda_{max}$ 253 mμ (log ε 3.97), is well superimposable with a syn-

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[*1] Hongo, Tokyo (日野 亨, 塩入孝之).

[1] J. Colonge, R. Chambard: Bull. soc. chim. France, **1953**, 982.

[2] *a*) A. E. Kellie, D. G. O'Sullivan, P. W. Sadler: J. Chem. Soc., **1956**, 3809. *b*) E. Wenkert, A. K. Bose, T. L. Reid: J. Am. Chem. Soc., **75**, 5514(1953).

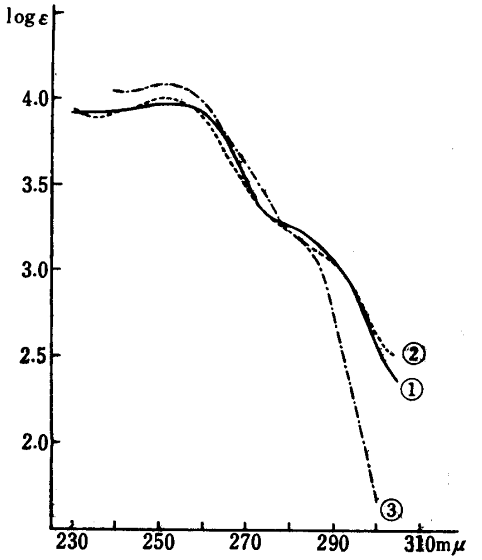


Fig. 1. Ultraviolet Absorption Spectra (in 95% EtOH)

① —— N,1-Dimethyl-2-oxo-3-indolineacetanilide (Ⅷ)

② ------ 1,3-Dimethyloxindole + N-methylacetanilide

③ -·-·- 1-Methylhydrocarbostyril[4] + N-methylacetanilide

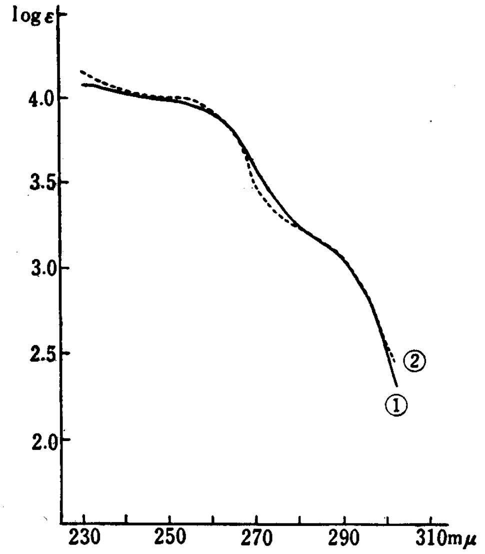


Fig. 2. Ultraviolet Absorption Spectra (in 95% EtOH)

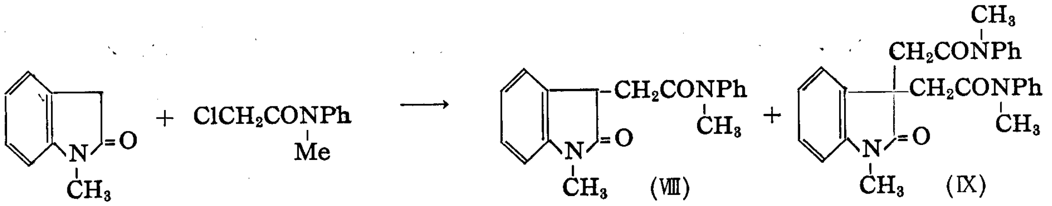
① —— N,N′,1-Trimethyl-2-oxo-3,3-indolinediacetanilide (Ⅸ)

② ------ N,1-Dimethyl-2-oxo-3-indolineacetanilide (Ⅷ) + N-Methylacetanilide

thetic curve obtained by summation of the curves of 1,3-dimethyloxindole[2a] and N-methylacetanilide.[3]

To confirm the oxindole skeleton in (Ⅷ), this was reduced by the Ladenburg method to an indole derivative.[5] A neutral oil, which showed positive Ehrlich reaction, was obtained, but this could not be purified and characterized.

Finally, the structure of (Ⅷ) was confirmed by synthesis.



Wenkert, *et al.*[6] reported that 1-methyloxindole could be monoalkylated with alkyl halides using sodium hydride in benzene. Following this procedure, 1-methyloxindole was alkylated with N-methyl-2-chloroacetanilide using sodium hydride in benzene. Two products were obtained after purification by chromatography over alumina. The one came as pale yellow prisms (Ⅷ), m.p. 107.5~109.5°, and was identified with (Ⅷ) obtained as above through admixture and infrared spectrum.

The other came as colorless needles, m.p. 136°, and its infrared spectrum showed two carbonyl bands (1717 and 1671 $cm^{-1}$). From the analytical data and molecular weight measurement it was assumed to be (Ⅸ). For further confirmation, (Ⅷ) was alkylated

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3) P. Ramart-Lucas: Bull. soc. chim. France, [5], **3**, 723(1936); P. Grammaticakis: *Ibid.*, **1949**, 134.

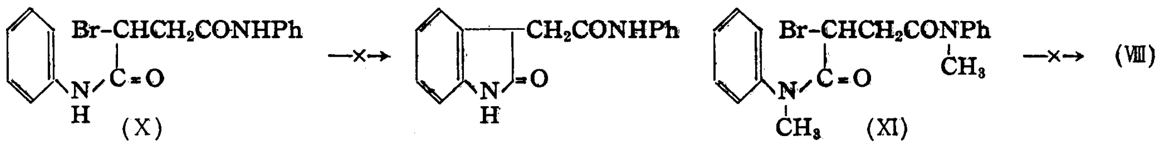
4) P. Ramart-Lucas, D. Biquard: *Ibid.*, [5], **2**, 1383(1935).

5) S. Sugasawa, M. Murayama: This Bulletin, **6**, 194(1958).

6) E. Wenkert, N.K. Bhattacharyya, T.L. Reid, T.E. Stevens: J. Am. Chem. Soc., **78**, 797(1956).

with N-methyl-2-chloroacetanilide and yielded a product, which was identified with (IX) through admixture and infrared spectrum. Thus, the structure of the cyclization product of (VII) with aluminium chloride was proved to be the oxindole derivative (VIII) and not a carbostyril (VIII').

Incidentally, attempts at Stollé-type cyclization of (X) and (XI) obtained by hydrogen bromide addition of fumaranilide and (VII) failed under various conditions.



## Experimental*[2]

**N,N'-Dimethylfumaranilide (VII)**—To a mixture of monomethylaniline (15.5 g., 0.145 mole) in dehyd. $Me_2CO$ (20 cc.) and anhyd. $K_2CO_3$ (25 g.), fumaryl chloride[7] (10.3 g., 0.067 mole) in dehyd. $Me_2CO$ (20 cc.) was added dropwise at $-5°$ to $-7°$ during 1 hr. After the addition, the mixture was stirred for 1.5 hr. at room temp., then kept overnight. The mixture was filtered, the residue was washed with hot $Me_2CO$ (100 cc.), and the filtrate and the washings were combined and evaporated. The resultant white solid was washed successively with 3% HCl (50 cc.), 10% HCl (2 × 50 cc.), $H_2O$, 10% $Na_2CO_3$ (100 cc.), and $H_2O$, and dried, giving (VII), m.p. 189~190° (17.4 g., 88.3%). Recrystallization from EtOH afforded colorless needles, m.p. 191° (reported[8] m.p. 187~188°). IR $\nu_{max}^{Nujol}$ $cm^{-1}$ : 1630 (CON<), 980 ($^{H}\!\!>C=C<_{H}$, *trans*).

**1-Methylcarbostyril (VI)**—A mixture of N-methylcinnamanilide (9.48 g., 0.04 mole) and powdered $AlCl_3$ (16.02 g., 0.12 mole) was heated in an oil bath with stirring, a vigorous reaction occurred at 55~60° (bath temp.). After cessation of the vigorous reaction, the dark brown mixture was heated at 95~105° (bath temp.) for 1 hr. When cooled, the whole mixture was poured onto crushed ice containing some HCl. The resultant precipitate was extracted with $CHCl_3$, which was dried and evaporated, giving crude (VI) as a brown solid (5.8 g., 91.2%), m.p. 60~68°. Purification from ligroine afforded colorless prisms, m.p. 73~74°, which was identical with that of an authentic specimen*[3] on admixture and in their IR spectra.

**N,1-Dimethyl-2-oxo-3-indolineacetanilide (VIII); Ring Closure of (VII) with Aluminium Chloride**—A mixture of (VII) (7.0 g.) and powdered $AlCl_3$ (70 g.) was heated at 230~235° for 5 hr. The resultant dark brown, viscous mixture was poured onto crushed ice (ca. 200 g.) containing 6 cc. of 10% HCl, separating a dirty brown precipitate which was extracted with benzene. The benzene solution was washed with $H_2O$, 10% $Na_2CO_3$, and $H_2O$, dried, and evaporated, giving 6.3 g. of a reddish brown oil. The oil was dissolved in EtOH, treated with charcoal, and the filtrate was evaporated. The residue was dissolved in benzene containing a small amount of hexane and decolorized with $Al_2O_3$. After removal of $Al_2O_3$, the filtrate was evaporated, giving 4.0 g. of brown oil which solidified on standing and melted at 94~102° (57.1%). Recrystallization from benzene-hexane afforded pure (VIII) as pale yellow prisms, m.p. 108.5~110°. *Anal.* Calcd. for $C_{18}H_{18}O_2N_2$ : C, 73.45; H, 6.16; N, 9.52. Found : C, 73.28; H, 6.48; N, 9.38; IR $\nu_{max}^{Nujol}$ $cm^{-1}$ : 1718, 1660 (CON<). UV $\lambda_{max}^{95\%\ EtOH}$ 253 mμ (log ε 3.97) (Fig. 1).

**Alkylation of 1-Methyloxindole; The Formation of (VIII) and (IX)**—To a suspension of NaH (0.24 g., 0.01 mole) in dehyd. benzene (1 cc.), 1-methyloxindole (1.47 g., 0.01 mole) in benzene (9 cc.) was added dropwise in $N_2$ stream at room temp. After the addition, the whole mixture was refluxed for 1 hr. and chilled with ice, giving a white pasty mixture. N-Methyl-2-chloroacetanilide (2.20 g., 0.012 mole) in benzene (4 cc.) was added dropwise to the above mixture. After stirring for 1 hr. at room temp., the mixture was refluxed for 9 hr., cooled, $H_2O$ and benzene were added, and the benzene layer was washed with $H_2O$ and dried. A yellow oil (3.23 g.) was obtained when the solvent was evaporated. The yellow oil was extracted with hot hexane (70 cc.) and the residue (1.43 g,) dissolved in benzene was chromatographed over $Al_2O_3$ (60 g.). From the effluent of benzene, a mixture of the starting materials was recovered (0.13 g.) and from the effluent of benzene-$CHCl_3$ (5:1), yellow prisms

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*[2] All m.p.s are uncorrected. Infrared spectra were taken by Koken Model DS-301 and ultraviolet spectra were taken by Beckman Model DU spectrophotometer.

*[3] The sample was donated by Dr. C. Kaneko of this Faculty, to whom the authors' thanks are due.

7) Org. Syntheses, Coll, Vol. III, 422.

8) W. H. Warren, M. R. Grose : J. Am. Chem. Soc., **34**, 1609(1912).

(0.43 g.) of m.p. 103~105° were obtained. From the hexane-soluble part, further crop of (VIII) (0.22 g.) was obtained by $Al_2O_3$ chromatography. On recrystallization it afforded pale yellow prisms, m.p. 107.5~109.5°, which showed no depression on admixture with (VIII) obtained from (VII) by $AlCl_3$.

From the effluent of benzene-$CHCl_3$ (3:1) of above chromatography, another kind of colorless needles (IX), m.p. 134~136° (0.76 g.), was obtained. Further crop (0.25 g.) was obtained from the hexane-soluble portion. Recrystallization from benzene-hexane afforded colorless needles, m.p. 136°. *Anal.* Calcd. for $C_{27}H_{27}O_3N_3$ : C, 73.45; H, 6.16; N, 9.52; mol. wt., 441.51. Found : C, 73.09; H, 6.33; N, 9.47; mol. wt. (Rast), 434. IR $\nu_{\max}^{\text{Nujol}}$ $cm^{-1}$ : 1717, 1671 (CON<). The UV curve was well superimposable with the synthetic curve obtained by summation of (VIII) and N-methylacetanilide as shown in Fig. 2.

**N,N′,1-Trimethyl-2-oxo-3,3-indolinediacetanilide (IX) : Alkylation of (VIII)**—To NaH (50 mg., 0.002 mole) suspended in anhyd. benzene (1.7 cc.), (VIII) (0.4 g., 0.00137 mole) in benzene (2.3 cc.) was added and the mixture was heated to reflux for 1.5 hr. When cooled, N-methyl-2-chloroacetanilide (0.35 g., 0.00119 mole) in benzene (2 cc.) was added and the whole was refluxed for 8 hr. To the cooled mixture, benzene and $H_2O$ were added, the benzene layer was washed with $H_2O$, dried, and evaporated, leaving a brown oil of crude (IX) (0.61 g.). It was chromatographed over $Al_2O_3$ (50 g.) and 0.55 g. (90%) of (IX), m.p. 130~131.5°, was obtained from the effluent of benzene-$CHCl_3$ (3:1) and $CHCl_3$. Recrystallization from benzene-hexane afforded colorless needles, m.p. 134~136°, which showed no depression on admixture and good identity of IR spectrum with (IX) obtained as above by direct dialkylation of 1-methyl-2-oxindole.

**2-Bromosuccinanilide (X)**—Into a suspension of fumaranilide (8.0 g.) in AcOH (60 g.), dry HBr gas was introduced under ice-cooling until HBr was saturated. After being kept at room temp. for 2 days, ca. 100 g. of AcOH was added to the mixture and HBr gas was again introduced into the mixture under ice cooling. The mixture was kept overnight, the resulting needle crystals were collected and washed with AcOH. Filtrate and washings were combined and poured into ice-water. The crystals that separated were collected. The two crops of crystals were recrystallized from MeOH, giving colorless needles, m.p. 205° (decomp.) (6.3 g. 60%). Repeated recrystallization from the same solvent raised the m.p. to 210° (decomp.). *Anal.* Calcd. for $C_{16}H_{15}O_2N_2Br$ : C, 55.33; H, 4.32; N, 8.07; Br, 23.05. Found : C, 55.61; H, 4.13; N, 8.86; Br, 21.91. IR $\nu_{\max}^{\text{Nujol}}$ $cm^{-1}$ : 3340 (NH), 1653 (CO-NH). It was subjected to Stollé's ring closure with $AlCl_3$ under various conditions. In milder condition, at 180°~210°, most of the starting material was recovered, while carbonization was observed at 260° (bath temp.).

**N,N′-Dimethyl-2-bromosuccinanilide (XI)**—HBr gas was introduced into the AcOH (30 cc.) solution of (VII) (4.0 g.) under ice cooling as above. After being kept for two days, the reaction mixture was poured into ice water, giving an oily product which solidified on stimulation. The solid was collected and dried, giving (XI) of m.p. 129~139° (0.8 g. 15.7%). Recrystallization from EtOH gave pure (XI) as colorless prisms, m.p. 146° (decomp.). *Anal.* Calcd. for $C_{18}H_{19}O_2N_2Br$ : C, 57.60; H, 5.07; N, 7.47; Br, 21.33. Found : C, 57.72; H, 4.89; N, 7.75; Br, 20.40. IR $\nu_{\max}^{\text{Nujol}}$ 1663 $cm^{-1}$ (CON<). It was subjected to Stollé's ring closure by heating at 180° with $AlCl_3$, but only the starting material was recovered.

The authors are grateful to Prof. Emeritus S. Sugasawa and Prof. S. Yamada for their encouragements and kind advices throughout this work. Thanks are also due to Mr. K. Tanikawa, Miss M. Ninomiya, and Miss E. Kobayashi for infrared spectral data, and to the members of Analysis Room of Tokyo Research Laboratory of Tanabe Seiyaku Co., Ltd. for microanalytical data.

## Summary

Cyclization of N,N′-Dimethylfumaranilide (VII) with aluminium chloride gave N,1-dimethyl-2-oxo-3-indolineacetanilide (VIII) and not a carbostyril derivative (VIII′). The structure of (VIII) was confirmed by the alkylation of 1-methyloxindole.

(Received December 28, 1959)