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The Reaction of Acetylenecarboxylic Acid with Amines. XVII.[1] The Addition of Dialkyl Acetylenedicarboxylates to Several Carcinogens

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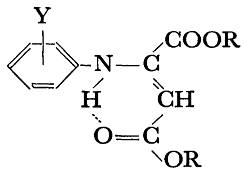
Synopsis. Hazardous carcinogens, α-naphthylamine (I), benzidine (II), 2′,3-dimethyl-4-aminoazobenzene (*o*-aminoazotoluene) (III), 2-amino-1-naphthol (IV), and 4-methylaminoazobenzene (V), easily reacted with esters of acetylenedicarboxylic acid (VI and VII) to give addition products, whose carcinogenicity could possibly be changed.

Since Rehn noticed, in 1895, three men with bladder tumors who all worked in the same dyestuffs factory, many cases of the hazards of handling α-naphthylamine (I), benzidine (II), and other aromatic compounds have been reported.[2] 2′,3-Dimethyl-4-aminoazobenzene (III),[3] 2-amino-1-naphthol (IV),[4] and 4-methylaminoazobenzene (V)[5] have also been established as carcinogenic substances.

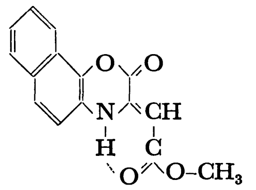
We have attempted the chemical modification of these hazardous compounds. It is conceivable that one can lessen or eliminate such a dangerous property by modification.

Dimethyl or diethyl acetylenedicarboxylate (VI or VII) reacted easily on admixture with these compounds. An addition reaction of an amino group onto the triple bond taking place, the primary amines, I, II, and III, gave the following fumarate-type compounds (VIII, IX, and X):



VIII: R = Methyl; Y = Benzo[*b*]
IX: R = Ethyl; *p*,*p*′-Linked dimer
X: R = Ethyl;
Y = *o*-Methyl-*p*-(*o*′-methylphenylazo)

In the reaction of IV, cyclocondensation followed the addition, forming a naphthoxazinone derivative (XI):



XI

Instead of the fumarate derivative, the secondary amine, V, afforded a compound of the succinate type (XII) upon the addition of two moles of V to the acetylenic bond. Except for XII, all the products are characterized by an intramolecular hydrogen bonding, as is evidenced by the IR (an absorption of ester carbonyl in the region 1674—1650 cm^{-1}) and NMR spectra.[6] Not only VIII, IX, and X, but also XI is similarly hydrogen-bonded between the ester carbonyl of the side chain and the amino group of the dihydrooxazine ring. This is one of the main structural changes as the carcinogenic amines (I, II, III, and IV) turn into the corresponding products.

All the reactions gave the adducts in high yield, proving themselves to be fit for the present purpose. These products are all new compounds; a carcinogenicity examination of them is awaited.[7]

Experimental

All the melting points are uncorrected. The IR spectra were recorded on a Nippon Bunko DS-301 or a Hitachi EPI-G3 spectrophotometer, while the NMR spectra were measured on a Hitachi H-60 spectrometer, using TMS as the external standard.

Dimethyl N-*(α-Naphthyl)aminofumarate (VIII).* Into a solution of I (0.3 g) in ethanol (10 ml), VI (0.3 g) was dropped with stirring. An exothermic reaction took place immediately, and the temperature of the reaction mixture rose to 25 °C from room temperature (21 °C). After the mixture had stood overnight, a small amount of water was added until it was turned turbid by yellow precipitates. The mixture was then left to stand in a freezer for several weeks. The crystals thus formed in an almost quantitative yield (0.6 g) were recrystallized from toluene to give pale yellow prisms; mp 69—70 °C. IR (nujol): 3242 (NH), 1736 (C=O), 1674 (chelated C=O), and 1612 (C=C) cm^{-1}. NMR (DMSO-d_6, δ): 3.57 (OCH$_3$), 3.72 (OCH$_3$), 5.41 (=CH–), and 10.17 (NH) ppm.

Found: C, 67.17; H, 5.30; N, 4.84%. Calcd for $C_{16}H_{15}O_4N$: C, 67.36; H, 5.30; N, 4.91%.

Tetraethyl Benzidine-N,N′-*difumarate (IX).* Obtained from II and VII in a similar manner. Yield, 91%. Yellow (dark) prisms from ethanol; mp 150—151 °C. IR (KBr): 3295 (NH), 1736 (C=O), 1662 (chelated C=O), and 1614 (C=C) cm^{-1}.

Found: C, 64.34; H, 6.08; N, 5.79%. Calcd for $C_{28}H_{32}N_2O_8$: C, 64.11; H, 6.15; N, 5.34%.

Diethyl 2′,3-Dimethyl-4-aminoazobenzene-N-*fumarate (X).* Obtained from III and VII. Yield, 87%. Orange prisms from methanol; mp 81—82 °C. IR(KBr): 3307 (NH), 1735 (C=O), 1662 (chelated C=O), and 1615 (C=C) cm^{-1}.

Found: C, 66.47; H, 6.40; N, 10.31%. Calcd for $C_{22}H_{25}O_4N_3$: C, 66.82; H, 6.37; N, 10.63%.

*3-(Methoxycarbonylmethylene)-3,4-dihydro-2*H-*naphtho[1,2-*b*]-1,4-oxazin-2-one (XI).* Obtained from IV and VI. Yield, 93%. Yellow fluorescent needles from methanol; mp 183—183.5 °C. IR (nujol): 3240 (NH), 1764 (lactone C=O), 1650 (chelated C=O), and 1623 (C=C) cm^{-1}. NMR (DMSO-d_6, δ): 3.77 (OCH$_3$), 5.69 (=CH–), and 10.91 (NH) ppm.

Found: C, 67.08; H, 4.36; N, 5.51%. Calcd for $C_{15}H_{11}O_4N$: C, 66.91; H, 4.12; N, 5.20%.

*Dimethyl 2,3-Bis[methyl(*p*-phenylazophenyl)amino]succinate*

(XII). Obtained from V and VI. Yield, 82%. Dark yellow crystals; mp 109—110 °C. IR (KBr): 1740 (C=O) cm^{-1}.

Found: C, 67.98; H, 5.82; N, 15.32%. Calcd for $C_{32}H_{32}O_4N_6$: C, 68.07; H, 5.71; N, 14.89%.

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